Rebecca Bascom, M.D. M.P.H.

RESEARCH ABSTRACT

Title of Project: **Mucociliary Clearance: A biomarker of sensitivity to sidestream tobacco smoke?**

Investigator(s): **Rebecca Bascom M.D. M.P.H., Principal Investigator**
David L. Swift Ph.D., Co-Investigator

Institution: **University of Maryland School of Medicine**
The Johns Hopkins School of Hygiene and Public Health

ABSTRACT: In the space below, please provide a descriptive summary of your proposed research project.

The long range goals of our research program are to understand the biological and physiological basis for differential sensitivity to common airborne irritants in the indoor environment, and to seek upper respiratory tract biomarkers of response and susceptibility to irritants. The most interesting finding of our current CIAR-funded research is that nasal mucociliary clearance is differentially altered following controlled sidestream tobacco smoke (SS) exposure in subjects with and without a history of subjective sensitivity to environmental tobacco smoke(ETS-S and ETS-NS). The overall objective of this proposal is to further characterize the effect of sidestream tobacco smoke(SS) on mucociliary clearance in these two subject groups. The hypothesis to be tested is that ETS-nonsensitive subjects demonstrate a reproducible acceleration of nasal mucociliary clearance after prolonged exposure to moderate levels of sidestream tobacco smoke, while ETS-sensitive subjects demonstrate unchanged or slowed clearance with focal collection of tracer in the anterior 2-3 centimeters of the nose. Specific aims are: 1. To further characterize the effect of SS exposure on mucociliary clearance with respect to its spatial distribution and intrasubject reproducibility, 2. To determine the exposure-response characteristics of altered mucociliary clearance in the upper respiratory tract following SS exposure, 3. To determine the time-response characteristics of the response to SS, 4. To develop a convenient method, appropriate for use in field studies, to assess mucociliary clearance in the upper respiratory tract. The method will use a nonradioactive, fluorescent aerosol coupled with nasal lavage and will be validated and characterized in anticipation of its applicability to field studies. We believe that the results of our work will address the Center's goals of investigating host susceptibility factors for effects due to inhalation of indoor contaminants, of developing convenient, objective ways to assess irritation and of developing methods to validate symptoms of irritation.

Rebecca Bascom M.D. 6-1-93

Signature, Principal Investigator Date

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CENTER FOR INDOOR AIR RESEARCH
1099 WINTERSON ROAD SUITE 280 LINTHICUM, MD. 21090
(410) 684-3777 FAX (410) 684-3729

APPLICATION FOR RESEARCH CONTRACT

1. PRINCIPAL INVESTIGATOR. NAME, TITLE, TELEPHONE # AND MAILING ADDRESS.

(A) Rebecca Bascom, M.D., M.P.H. (NAME) (B) Associate Professor (TITLE) (C) (410)706-8162 FAX (410)706-2169 (TELEPHONE #/ FAX #)

(D) Medicine (DEPARTMENT) (E) University of Maryland School of Medicine (INSTITUTION)

(F) 10 South Pine Street, Suite 800, Baltimore (MAILING ADDRESS) (G) Maryland 21201 (STATE/ZIP)

2. PROJECT TITLE. Mucociliary Clearance: A biomarker of sensitivity to sidestream tobacco smoke?

3. KEY WORDS. PLEASE PROVIDE THREE (3) KEY WORDS WHICH WILL BE USED AS REFERENCE HEADINGS.
Tobacco Smoke, Mucociliary Clearance, Biomarkers

4. INSTITUTION. NAME AND ADDRESS OF INSTITUTION RESPONSIBLE AND ACCOUNTABLE FOR DISPOSITION OF FUNDS AWARDED ON THE BASIS OF THIS APPLICATION.

(A) Univ. of Md. at Baltimore (INSTITUTION) (B) 511 West Lombard Street, 5th Floor (STREET ADDRESS)

(C) Baltimore (CITY) (D) Maryland 21201 (STATE/ZIP)

5. LOCATION. LIST LOCATION WHERE RESEARCH WILL BE CONDUCTED *IF OTHER THAN INSTITUTION IDENTIFIED IN #4 ABOVE*

(A)

(B)

6. INCLUSIVE DATES AND TOTAL COSTS OF THIS SPECIFIC PROJECT RELATED TO EACH 12 MONTH PERIOD IF MORE THAN ONE YEAR IS REQUIRED TO COMPLETE PROJECT. SUMMARIZE FROM BUDGET PAGE, ITEM 12(J). IT MUST BE UNDERSTOOD THAT AWARDS FOR 2ND AND 3RD PERIODS ARE DEPENDENT ON CENTER APPROVAL OF CONTINUATION APPLICATION.

	INCLUSIVE DATE			TOTAL COST
(A) 1ST 12 MONTH PERIOD	01/01/94	THRU	12/31/94	$ 181,746
(B) 2ND 12 MONTH PERIOD IF REQUIRED	01/01/95	THRU	12/31/95	$ 180,469
(C) 3RD 12 MONTH PERIOD IF REQUIRED	01/01/96	THRU	12/31/96	$ 183,481

7. INSTITUTIONAL OFFICER. NAME, TITLE AND TELEPHONE NUMBER OF INDIVIDUAL AUTHORIZED TO SIGN FOR THE INSTITUTION IDENTIFIED IN #4 ABOVE. IT IS UNDERSTOOD THAT THE OFFICER, IN APPLYING FOR A CONTRACT, HAS READ AND FOUND ACCEPTABLE THE CENTER'S MANAGEMENT OF RESEARCH CONTRACTS AND CONTRACT ADMINISTRATION POLICY.

(A) Janet B. Simons (NAME) (B) Contract & Grant Administrator (TITLE)
(C) (410)706-3559 (TELEPHONE) (D) Janet B. Simons (SIGNATURE OF INSTITUTIONAL OFFICER) (B) 06/01/93 (DATE)

8. PRELIMINARY STUDIES*
(A) FEASIBILITY OF PROPOSED RESEARCH
(B) QUALIFICATIONS OF INVESTIGATOR

9. EXPERIMENTAL PLAN*
(A) DESIGN
(B) METHODS
(C) ANALYSIS OF DATA
(D) INTERPRETATION OF RESULTS
(E) TIMETABLE FOR THE INVESTIGATION.
(F) LITERATURE CITED

10. AVAILABLE FACILITIES AND RESOURCES.

11. OTHER SUPPORT

* APPEND AS MUCH MATERIAL AS REQUIRED. TYPE, SINGLE SPACE, USE 8-1/2 X 11" WHITE PAPER AND LABEL EACH SHEET WITH NAME OF THE PRINCIPAL INVESTIGATOR IN THE UPPER RIGHT HAND CORNER AND PAGE NUMBER AT THE BOTTOM. CONSECUTIVELY NUMBER EACH ADDENDUM BEGINNING WITH PAGE 5. DO NOT INSERT PAGES BETWEEN PAGES 1 AND 6, E.G., 2A, 2B, 3A, ETC. INCLUDE NINE COPIES AND AN ORIGINAL. IF SENDING PHOTOGRAPHS, INCLUDE 2 ORIGINAL SETS. NOTE: EACH OF THE NINE COPIES MUST BE PLACED IN A BINDER PER MAILING INSTRUCTIONS.

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R: REDACTED MATERIAL

Bascom, Rebecca

12.BUDGET. Detailed specific needs for the first 12-month period. Estimate category sub-totals for 2nd and 3rd periods, if required. Append justifications.

(a) Salaries, List personnel by name and title. Indicate individuals % time to be spent on this project.	$ 1st period	$ 2nd period	$ 3rd period
% Professional:			
25 Rebecca Bascom, M.D., M.P.H. Assoc. Professor of Medicine			
10 Thomas Permutt, Ph.D. Assist Prof Epid & Prev Med			
% Technical:			
50 Thomas Fitzgerald, B.S. Research Assistant			
10 Larry Sauder, B.S. Research Specialist			
% Other:			
10 Ruth Ann Rochlitz Secretary			
Fringe benefits payable at institution's rate of 30 %			
Category (a) Sub-Total			
(b) Consultants (per diem, travel & expenses): Donovan B. Yeates, Ph.D. Lida B. Wong, Ph.D.			
Category (b) Sub-Total			
(c) Supplies & Expense: Consumables (by category) Cigarettes & ETS Generator Supp. Nicotine Sorbent Tubes & Analysis Cal. Gases & Misc. Lab Supplies			
Animals and related costs			
Other expenses (itemize) See budget justification			
Category (c) Sub-Total			
(d) Travel Expenses: ATS/ALA International Conf. Am. Acad. of Allergy & Immun Mtg.			
Category (d) Sub-Total			
(e) Alterations and Renovations			
Category (e) Sub-Total			
(f) Sub-contracts David Swift, Ph.D. Johns Hopkins Univ			
Category (f) Sub-Total			
(g) Equipment Collimated Scint. Detector, CO Analyzer			
Category (g) Sub-Total			
(h) TOTAL DIRECT COSTS			
(i) Indirect costs not to exceed 25% of the sum of (a) thru (f):			
(j) TOTAL PROJECT COSTS			

REDACTED

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BUDGET JUSTIFICATION

Personnel:

The principal investigator for this research project is Rebecca Bascom, M.D. M.P.H. Support personnel include T. Fitzgerald, L. Sauder, R.A. Rochlitz and Dr. Swift and his staff at Johns Hopkins (sub-contract).

Dr. Bascom (25% effort) is an associate professor of medicine and Director of the Environmental and Airway Disease Research Facility at the University of Maryland. She will be responsible for all aspects of the study and will collaborate with Dr. Swift at Johns Hopkins who has expertise in aerosol deposition and mucociliary clearance.

Mr. Fitzgerald (50% effort), a registered cardiopulmonary technologist, holds the position of research assistant at the University of Maryland. He will be responsible for all technical aspects of the project including generation and monitoring of the environmental tobacco smoke (ETS), volunteer recruitment, performing the nasal resistance measurements, chamber maintenance, data analysis, and assisting Dr. Swift's staff with aerosol administration and clearance measurements.

Mr. Sauder (10% effort), is a registered respiratory therapist and cardiopulmonary technologist who is a research specialist at the University of Maryland. He will be responsible for quality assurance, procurement of equipment and supplies, and budget management.

Ms. Rochlitz (10% effort) is a secretary at the University of Maryland. She will be responsible for general duties associated with the project including volunteer recruitment, manuscript preparation, and typing correspondence and reports.

All salaries were increased by 4% per year. Fringe benefits are requested at the institutional rate of 30%.

Consultant Costs:

Donovan Yeates,Ph.D., and Lin B. Wong, Ph.D. will serve as consultants throughout the project and make one trip per year to the University of Maryland to review the work being done and to exchange scientific ideas. These two scientists each have unique and complementary expertise. Each of these investigators has an active research program in mucociliary clearance using animal and in vitro models to explore the control of and determinants of mucociliary clearance in the respiratory tract. Their consultation will enhance the conceptual review of our study results and allow rapid transfer of new understanding of

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the mechanisms of alteration of mucociliary clearance from animal to human studies. Dr. Yeates pioneered techniques to measure ciliary beat frequency in animal models and will provide technical and conceptual review of the physiolgoic mechanisms involved in our study results. Dr. Wong has funded research on the intracellular mechanisms controlling ciliary beat frequency. He is currently working to develop a technique to assess ciliary beat freqeuncy in vivo in the human nose. His consultation on this project will allow us to have input onto aspects of that development project, and to determine when the technique is ready to use in our system.

Supplies & Expenses:

The consumables include:

- $300 for cigarettes - ETS generation
- $780 for ETS generator parts - The ETS generator parts (valves, tubing, pumps, etc.) in the mainstream portion of the generator need to be replaced frequently to prevent clogging.
- $1,520 for XAD-4 sorbent tubes & nicotine analysis - Nicotine samples will be taken with each exposure and analyzed by Baltimore Spectral Services. This includes $80 for a case of tubes plus $45/sample X 32 samples.
- $320 for CO and organic calibration gases - The level of ETS generated will be monitored by two CO monitors (Bendix and Drager), a particle counter (Climet) and a total organic vapor monitor (HNU-PI101, HNU, Inc. Charlement, MA). The CO and total organic vapor monitors are calibrated daily.
- $500 for miscellaneous supplies - These include skin test supplies, methacholine for bronchial provocation, mouthpieces, and general lab supplies.

The other expenses include:

- $4,160 for volunteer payments and advertising - This cost includes screening 40 volunteers at $40/volunteer, studying 16 volunteers at $150/volunteer, and advertising cost of $160.
- $510 for computer/office supplies and telephone (long distance calls only)
- $1,500 for chamber and instrumentation maintenance/repair - Past experience has shown a need to budget for unforseen repairs to the environmental chamber, the occurrence and nature of the breakdowns and their associated repair cost can not be determined ahead of time. The Climet particle counter also requires frequent factory maintenance (cleaning and calibration) at a cost of $800 per visit.
- $1,000 for illustrative services, publication costs, and reprints.

All costs were increase by 4% per year with the exception of the volunteer costs and the XAD-4 sorbent tubes & nicotine analysis. These costs were based the actual number of volunteers to be studied and the number of exposure days.

Travel & Expenses:

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Travel is anticipated for abstract presentation at the American Thoracic Society/American Lung Association International Conference and the American Academy of Allergy and Immunology Meetings. Travel expenses for years 2 and 3 were increased by 4% annually.

Sub-Contracts:

David Swift, Ph.D. from Johns Hopkins University who has extensive experience in aerosol deposition and mucociliary clearance will serve as co-investigator on this project. He will be responsible for the design and construction of the new scintillation detector with input from Dr. Bascom. See the appended sub-contract budget and justification.

Equipment:

A Drager Model 190 CO Monitor ($800) is being requested so that the CO level in the exposures can be measure simultaneously by two monitors. This is necessary for volunteer safety and to guarantee ETS uniformity in the room. One of our two current CO monitors, (an Ecolyzer) is outdated, and is no longer being supported by the manufacturer for repairs. We recently replaced the sensor, and will not be able to replace it again (expected duration of useful function 6-12 months)

A Collimated Scintillation Detector ($9,590) is required to measure the mucociliary clearance of the Tc99 sulfur colloid aerosol.

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Bascom, Rebecca

JOHNS HOPKINS
UNIVERSITY

School of Hygiene and Public Health
615 North Wolfe Street
Baltimore MD 21205
(410) 955-3602 / FAX (410) 955-9334
Division of Environmental Health Engineering

May 27, 1993

Rebecca Bascom, M.D.,MPH
Div. of Pulmonary & Critical Care Medicine
University of Maryland School of Medicine
10 S. Pine St.
Baltimore, MD 21201-1192

Dear Dr. Bascom:

This letter is to confirm my strong interest in participating as a collaborating investigator on the proposed research project to CIAR entitled "Mucociliary Clearance: A Biomarker of Sensitivity to Sidestream Tobacco Smoke?"

I believe that the research we have carried out in our laboratory on upper respiratory response to environmental agents has led to the development of skills and techniques which can be usefully applied to the proposed research. Our joint efforts on the first phase of the study of the nasal effects of exposure to SST has been very productive and I look forward to the continued collaboration.

I believe this research program will contribute important information to the understanding of the health effects of environmental tobacco smoke at realistic environmental concentrations.

A subcontract covering the Johns Hopkins University costs for the proposed research effort is appended to this letter.

Sincerely,

David L. Swift

David L. Swift, Ph.D.
Professor

Herbert R. Hansen, Jr.,MBA, CPA
Sr. Assoc. Dean for Finance and Admin.

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Subcontract to University of Maryland School of Medicine
"Mucociliary Clearance: A Biomarker of Sensitivity to Sidestream Tobacco Smoke?"

BUDGET

Year One (1/1/94 - 12/31/94)

Personnel	% Effort	Salary	F.B. (29.5%)	Total Cost
David L. Swift, Ph.D., Investigator	15	12,600	3,717	$16,317
Jana Nadarajah, Research Tech.	75	15,000	4,425	19,425
Sandra Hayes, Adm. Asst.	6	1,110	328	1,438
Total Personnel Costs				**$37,180**
Laboratory Supplies				3,000
Total Direct Costs				40,180
Indirect Cost Recovery (25%)				10,045
Total Costs (Year One)				**$50,225**

Year Two (1/1/95 - 12/31/95)

All Direct Costs Increased 4%	
Total Direct Costs	**41,787**
ICR (25%)	10,447
Total Cost (Year Two)	**$52,234**

Year Three (1/1/96 - 12/31/96)

All Direct Costs Increased 4%	
Total Direct Costs	43,458
ICR (25%)	10,864
Total Cost (Year Three)	**$54,322**

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BUDGET JUSTIFICATION

Personnel

David L. Swift, Investigator. Dr. Swift will participate in all aspects of the research program. He will be involved in the technical development, implementation, interpretation of results, design of follow-up studies, and preparation of material for publication. He will provide particular guidance with respect to the techniques of aerosol surface bolus placement, measurement of spatial distribution of deposited and cleared particles, and the development of the field technique for spatially selective lavage of the nasal passage. Nasal anterior casts for particle clearance zones will be carried out under his guidance.

Jana Nadarajah, Research Technician. Ms. Nadarajah will have chief responsibility for carrying out the studies at Johns Hopkins as a part of the research effort and will give major assistance to the studies of smoke exposure and clearance at the University of Maryland. She will carry out these research responsibilities as a part of her work as a part time doctoral student and will thus be involved in the interpretation of the research results and their preparation for publication and presentation at scientific meetings.

Sandra Hayes, Administrative Assistant. Ms. Hayes will carry out all clerical and administrative responsibilities in connection with the subcontract.

Supplies

Laboratory and Office Supplies. The research proposal identifies a number of special laboratory supplies and chemical substances which must be purchased in order to carry out the research activity at Johns Hopkins. These include tantalum, casting polymer, lavage fluids, chemical markers (e.g., fluorescent materials) for clearance measurement, and radioisotopes. These consumable laboratory supplies also include the means for administering the particles to the nasal passages (e.g. nebulizers) and retrieving them by lavage by simple devices which can be employed in the field. A small portion of the supply money must also provide for necessary office costs, such as photocopying, etc.

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13. BIOGRAPHICAL SKETCH of all professional personnel listed in 12(a). Append Please include the following. Name, title, education, scientific field, major research interest, research and/or professional experience and publications. (Limit list of publications to the 20 most important and/or relevant.)

14. a) Are HUMAN SUBJECTS to be used in this research? X Yes _____ No
If yes, attach Institutional Review Board approval for procedures involving human subjects.

b) Are LABORATORY ANIMALS to be used in this research? _____ Yes X No
If yes, attach Institutional Animal Care and Use Committee approval for procedures involving animals.

15. SIGNATURE OF PRINCIPAL INVESTIGATOR: It is understood that the applicant in applying for a Contract has read and found acceptable the Statements of Policy and Terms Under Which Project Contracts Are Made appearing in the application package.

Rebecca Bascom (MD) 05/26/93

Signature of Principal Investigator Date

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8. PRELIMINARY STUDIES

A. Feasibility of Proposed Research

The feasibility of the proposed research will be presented by providing an introduction and preliminary data, and by presenting and justifying specific aims and hypotheses.

I. Introduction

Differential sensitivity to common airborne irritants in the indoor environment is well recognized but an understanding of the biological and physiological basis for it is lacking [1]. An irritant is defined as any agent that causes symptoms of irritation or that induces inflammation. Excluded are corrosives (whose primary action is through tissue destruction) and allergens (which act through a specific immune response). Forty percent of the chemicals in the NIOSH Pocket Guide to Chemical Hazards are listed as causing upper respiratory irritation[2]. Many of the agents that have been identified in the indoor environment are irritants, including volatile organic compounds (VOCs), environmental tobacco smoke (ETS) and non-allergenic bioaerosols. Nearly one-third of a group of office workers reported that they considered themselves especially sensitive to common indoor irritants[3].

Upper respiratory symptoms typically predominate when health concerns are expressed in indoor environments[4], yet objective verification of the symptoms is difficult. Field studies of indoor air quality problems are limited by the paucity of methods available to characterize the upper respiratory tract. There remains a critical need for well-characterized upper respiratory tract biomarkers of response and susceptibility to irritants in the indoor environment[1].

Mucociliary clearance is a biologic marker of the upper respiratory tract. Normal mucociliary clearance reflects the integrated functioning of cilia, glandular and serous cell secretion, and proper regulation of airway surface fluid. Mucociliary clearance is a key component of "natural immunity"[6], i.e. the nonspecific portion of the immune system, because it removes toxic, infectious, or allergenic particles from the airway surface[7].

Mucociliary clearance can be altered by exposure to irritants. Studies in the tracheobronchial tree of humans and animals have demonstrated a biphasic effect of inhaled irritants on respiratory tract mucociliary clearance: low levels of irritants accelerate mucociliary clearance, while high levels of irritants inhibit mucociliary clearance[8-16]. The biphasic effect of irritants on mucociliary clearance can be broadly conceptualized in two ways. First, exposure to irritants initiates two competing sets of responses: those that accelerate and those that retard mucociliary clearance. The observed effect on mucociliary

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[1]The National Research Council defines a **biologic marker of a response** as "any change that is qualitatively or quantitatively predictive of health impairment or potential impairments associated with exposure. Biological markers are also useful to identify endogenous components or system function that are considered to signify normal health." The Council defines a **biologic marker of susceptibility** as one that indicates "individual or population differences that affect the biologically effective dose of or the response to environmental agents independently of an exposure under study....Such markers include ...low organ reserve capacity...or other identifiable genetically determined or environmentally induced variations in absorption, metabolism and response to environmental agents...The reserve capacity of an organ to recover from an insult at the time of exposure can play an important role in determining the extent of an impairment." [5]

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clearance is the net effect of the two responses. An alternate concept is that accelerated mucociliary clearance is the normal compensatory response to irritant exposure, and that inhibition of mucociliary clearance only occurs when this compensatory reserve is exhausted .

Studies of nasal mucociliary clearance have shown that clearance is reduced with exposure to SO_2, is increased with exercise or alpha adrenergic agonists, and is unchanged with temperature and humidity[17-20]. Workers chronically exposed to wood dust, grain silo dust or hair spray were demonstrated to have impaired mucociliary clearance[21]. The epidemiologic study of Broder et al that characterized health effects in residents of homes insulated with ureaformaldehyde foam insulation (UFFI)[22]. The presence of a wide variety of symptoms correlated with the presence of squamous metaplasia on nasal biopsy specimens. The investigators did not characterize mucociliary clearance in this study, however, the presence of squamous metaplasia (at a site in the nasal passage where a pseudostratified ciliated columnar epithelium was present in control subjects) would be expected to impair mucociliary clearance.

What is the relationship between mucociliary clearance and symptoms of irritation? Twenty years ago, Andersen et al related mucous flow rates during clean air exposure with subjective discomfort during SO_2 exposure. Reduced baseline mucociliary clearance was associated with increased subjective discomfort sensation during controlled SO_2 exposure[23]. These investigators suggested that the "mucus flow rate in clean air might be used to predict subjective discomfort sensations during SO_2 exposures"[23]. Further exploration of this possibility did not occur, however. Broder's study, cited above, suggests that alterations of nasal epithlial morphology (with loss of ciliated cells) are associated with chronic troublesome symptoms.

The long range goals of our research program are to understand the biological and physiological basis for differential sensitivity to common airborne irritants in the indoor environment, and to seek upper respiratory tract biomarkers of response and susceptibility to irritants. The purpose of this grant is to advance our understanding of the relationship between baseline mucociliary clearance, historical upper respiratory tract sensitivity to irritants, and the effect of acute irritant exposure on symptoms and mucociliary clearance. We will use as our model upper respiratory sensitivity to environmental tobacco smoke.

Previous investigators have described mucociliary function in the upper respiratory tract using one of several methods[5]. One common test of mucociliary clearance, the saccharine test, involves placement of a small volume of saccharine on the inferior turbinate, and recording the interval required for the subject to experience a sweet taste on the back of the tongue[24]. Frances et al placed multiple radioactive beads on the turbinate[25] while Saketkhoo placed radioopaque Teflon discs mixed with bismuth trioxide[17]. Proctor and Andersen used a single radioactive bead placed on the inferior turbinate, and calculated the velocity of its posterior passage using a series of vertical, collimated slits[7]. Using the latter technique, the investigators concluded that rates of baseline mucociliary clearance vary widely among individuals, but that a single individual's rate of mucociliary is reproducible over time.

Recent animal studies have pointed out the need to rethink the techniques for measuring mucociliary clearance in humans. Animal studies have elegantly demonstrated that the effects of irritants on the upper respiratory tract mucosa are non-uniformly distributed[26-28]. The implications of this finding are that sensitive measurement of mucociliary clearance should include a more dispersed placement of an aerosol in the nose, rather than the focal placement of a single bead or drop of liquid. Furthermore, assessment of effects of an irritant on the anterior aspects of mucociliary clearance is desirable. Studies by Andersen reported that controlled challenge with formaldehyde at 0.25, 0.4, 0.8 and 1.6 ppm caused a decrease in nasal mucus flow, with the decrease being greatest in the anterior part of the nose[29]. The method

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of Saketkhoo only investigates mucociliary clearace in the middle section of the nose and would be unable to detect effects localized to the anterior part of the nose[17].

The development and characterization of an improved, simple tool to profile upper respiratory mucociliary clearance represents an important step in being able to describe the physiology of the upper respiratory tract mucosa and altered function caused by indoor pollutants. Drs. Swift, Bascom and colleagues are an effective interdisciplinary team to continue to develop this method, since they combine expertise in aerosol generation and delivery, expertise in clinical research, and knowledge of biological and physiological methods of assessment of the upper respiratory tract.

II. PRELIMINARY DATA:

Environmental tobacco smoke(ETS) is primarily comprised of the smoke emitted from the burning end of the cigarette (sidestream tobacco smoke, or SS) and exhaled mainstream smoke (MS). SS and MS differ in their composition, but SS is the predominant component of ETS, and is considered a reasonable surrogate for controlled exposure studies.

We have chosen controlled human studies of SS as a model with which to study differential acute responsiveness to irritants for several reasons: subjects can readily be found with a differential symptom profile on historical ETS exposure; methods for smoke generation and exposure are well developed; and animal studies demonstrate that the acute response to smoke in the upper airway occurs via activiation of c-fiber neurons indicating that this may serve as a useful model for irritant responsiveness in general. Finally, ETS is a common indoor air pollutant, and health effects research in ETS remains of clinical and public health importance.

Our broad hypothesis is that reported sensitivity to irritants is associated with objective evidence of altered function following irritant exposure. The general strategy of our research program has been to stratify subjects based on their history of responsiveness to a environmental irritant, and to perform controlled challenge studies coupled to a range of endpoints. Physiologic endpoints have included: posterior rhinometry with assessment of nasal resistance and maximum inspiratory flow; and acoustic rhinometry with assessment of cross-sectional diameter and nasal volume. Biologic endpoints have been measured by sampling the nose (by nasal lavage or nasal scrapings) and enumerating cells or quantifying mediators or proteins in lavage fluid. Nasal mucociliary clearance has been measured by administering a ^{99m}Tc-sulfur colloid aerosol, and recording clearance with a scintillation detector .

Initial studies at the University of Maryland Environmental Research Facility characterized historical symptoms related to environmental tobacco smoke in healthy young adults. Of a group of 77 healthy non-smoking subjects, 40% reported a history of one or more rhinitis symptoms following ETS exposure while 25 % reported a history of nasal irritation[30]. These data indicated that subjects with and without ETS-related upper respiratory symptoms were common in the general population and would be accessible for study.

The subject profile of a group studied recently is shown below. This profile illustrates our selection criteria, and several features common to our studies over the last several years: first, we select subjects based on their history of ETS-rhinitis, however these individual also report increased irritation with smoke exposure as well; second, the characteristic of ETS-sensitivity occurs among individuals of both genders, and in both atopic and nonatopic subjects. Generally speaking, ETS-sensitivity is more common among women and atopic subjects.

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Table: Subject Characteristics

	ETS Sensitive (ETS-S)	ETS Nonsensitive (ETS-NS)
Sample size (N)	13	16
Age (years)	24±1.6	25±0.7
Gender (M/F)	3/10	7/9
Atopic (Y/N)	9/4	8/8
Number of positive skin tests	2.7±0.8	2.6±0.8
ETS-Rhinitis Index*	5.7±2.3***	0.7±0.5
ETS-Irritation Index*	9.9±4.1**	5.4±3.9

*A screening questionnaire asked subjects to rate the history and severity of symptoms which had occurred with past ETS exposure . Symptoms were scored on a 0-5 scale: 0=symptom absent, 1=mild, 3=moderate, 5=severe. The ETS-Rhinitis Index was calculated as the sum of rhinorrhea, nasal congestion, post-nasal drip and sneezing. Subjects are defined as ETS-Sensitive (ETS-S) if they have an ETS-Rhinitis Index > 2. Subjects are defined as ETS-Nonsensitive(ETS-NS) if they have an ETS-Rhinitis Index ≤ 1. The ETS-Irritation Index was calculated as the sum of eye irritation, nose irritation, throat irritation and headache. Subjects were defined as atopic if one or more of a screening battery of skin prick tests showed a positive result.

**p<0.01, ETS-S vs. ETS-NS

***p=0.0001, ETS-s vs. ETS-NS

Our controlled human challenge studies with sidestream tobacco smoke have demonstrated the following findings: ETS-sensitive subjects typically report higher symptom rates than ETS-NS subjects during controlled challenge with SS. Exposure to brief, high levels of smoke (45 ppm CO, 15 minutes) causes increased nasal resistance in ETS-S but not in ETS-NS subjects[30]. The increased nasal resistance is likely due to vascular congestion since it is blocked by pretreatment with alpha adrenergic agonists (R. Bascom, unpublished data). Increased vascular permeability does not occur, as evidenced by unchanged levels of albumin, kinin and TAME-esterase activity in nasal lavage fluid at the time of nasal congestion[30]. This feature of the human irritant response distinguishes it from the rodent irritant response in which increased vascular permeability occurs readily. Although subjects described themselves as being "allergic to tobacco smoke", an IgE mechanisms is unlikely as evidence by unchanged levels of histamine in nasal lavage fluid. Exposure to more prolonged, moderate levels of SS (15 ppm CO, 1 or 2 hours) causes nasal congestion in both ETS-S and ETS-NS subjects. However, when the particle phase is removed from the SS, and subjects are exposed to the vapor phase alone, only ETS-S subects demonstrate congestion[31]. These data suggest that the ETS-S subjects are more responsive to the organic vapor phase component of the SS than are the ETS-NS subjects. There is no correlation between a biomarker of exposure to SS (urinary cotinine) and the nasal congestive response, indicating the the increased responsiveness to SS is not due to subjects receiving an increased dose of SS. Acoustic rhinometry has been used to look at the anatomic correlates of the nasal congestive response to SS, and has demonstrated that a reduced cross-sectional area occurs throughout the nasal cavity, including a reduction in the minimum cross sectional area, located in the anterior part of the nasal cavity. Time course studies have shown that the congestive response generally resolves within one hour, and there is no evidence of a late phase response.

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During the past year, we determined the effect of exposure to sidestream tobacco smoke on upper respiratory mucociliary clearance in ETS-S and ETS-NS subjects. The experimental design of these studies is shown below. Six ETS-S and six ETS-NS subjects were exposed on two days, separated by at least two weeks, to clean air or STS (15 ppm CO) for one hour. Outcome measures for the study included assessment of symptoms, posterior rhinometry, acoustic rhinometry, nasal particle deposition, and nasal mucociliary clearance. Only the methods for mucociliary clearance and the data on the effects of SS on clearance will be presented here.

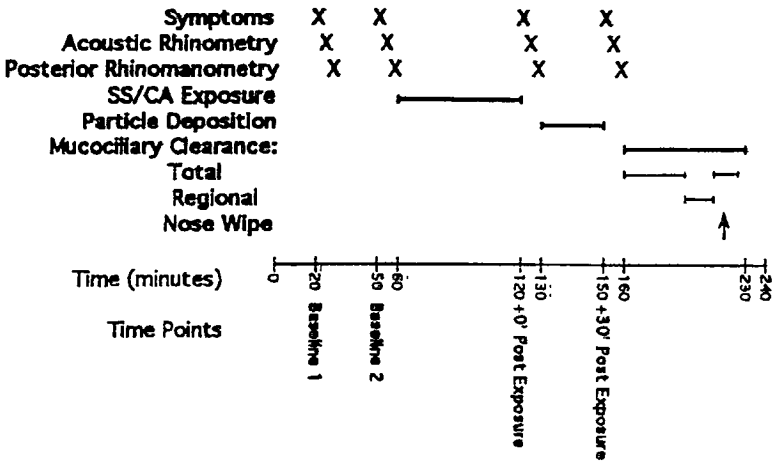

Figure: Protocol for studies of the effect of sidestream tobacco smoke on nasal mucociliary clearance

Mucociliary clearance was assessed by administering an aerosol of ^{99m}Tc-sulfur colloid into the nose using a DeVilbus 40 nebulizer. Preliminary studies indicated that placement of the delivery tube 0.2 cm anterior to the edge of the inferior turbinate resulted in reproducible clearance rates. Clearance was assessed using a sodium iodide-thallium crystal scintillation detector, counting for 30 seconds every two minutes. The dose of ^{99m}Tc-sulfur colloid was scaled to deliver an average of 10,000 counts/30 seconds against a background of 250 counts/30 seconds. Counting for the first 40 minutes, and 55-69 minutes after aerosol adminstration was performed with the scintillation detector positioned "en face", i.e. anterior to the subject's nose (see Figure). Consistent placement was ensured by constructing a sculpted facepiece and aligning marks on the facepiece and the subject's face.

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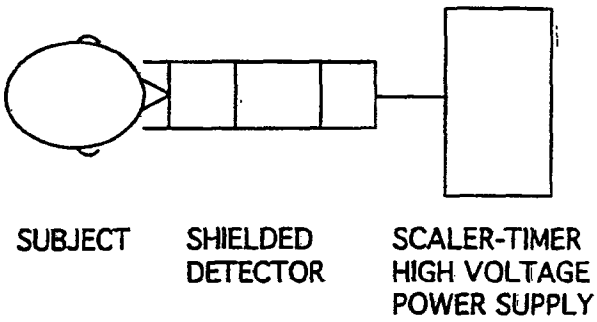

Figure: Orientation of the subject and the scintillation detector for measurement of total mucociliary clearance

The results are shown in the Figure below. ETS-NS and ETS-S subjects demonstrated similar average rates of mucociliary clearance under conditions of clean air pre-exposure. After controlled SS exposure, ETS-NS subjects demonstrated accelerated mucociliary clearance after controlled smoke exposure while ETS-S subjects as a group show no acceleration of mucociliary clearance.

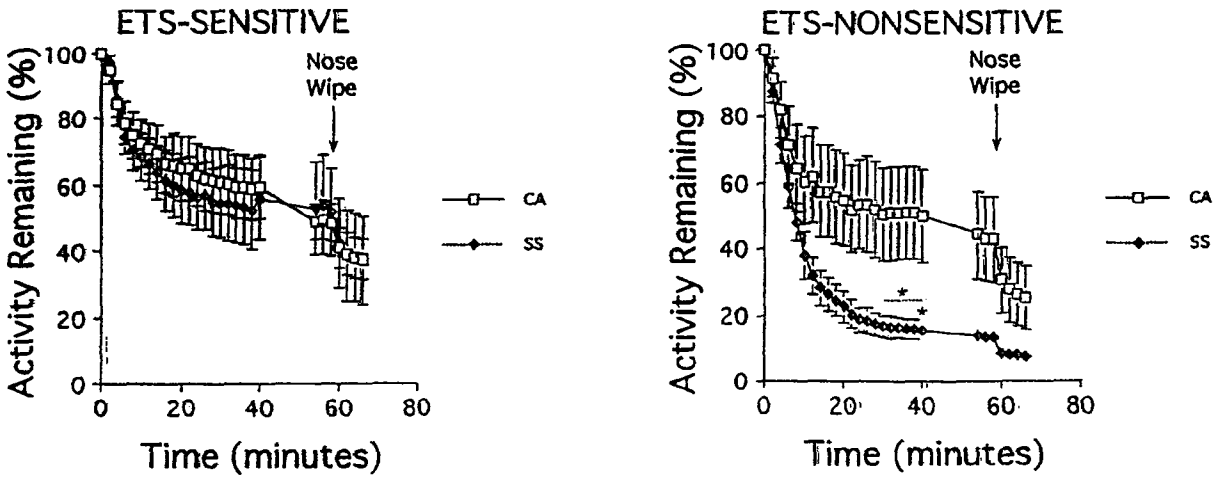

Figure: Effect of exposure to sidestream tobacco smoke (SS) or clean air (CA) on nasal mucociliary clearance in ETS-sensitive and ETS-nonsensitive subjects. See text above for description of protocol

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Individual subject results are shown for the percent clearance at 40 minutes after administration of the tracer. ETS-NS subjects either demonstrated acceleration of clearance or maintained rapid mucociliary clearance with both air and SS exposure. ETS-S subjects either showed an intermediate level of acceleration or a reduction in rates of mucociliary clearance. The study was repeated in two subjects with consistent results.

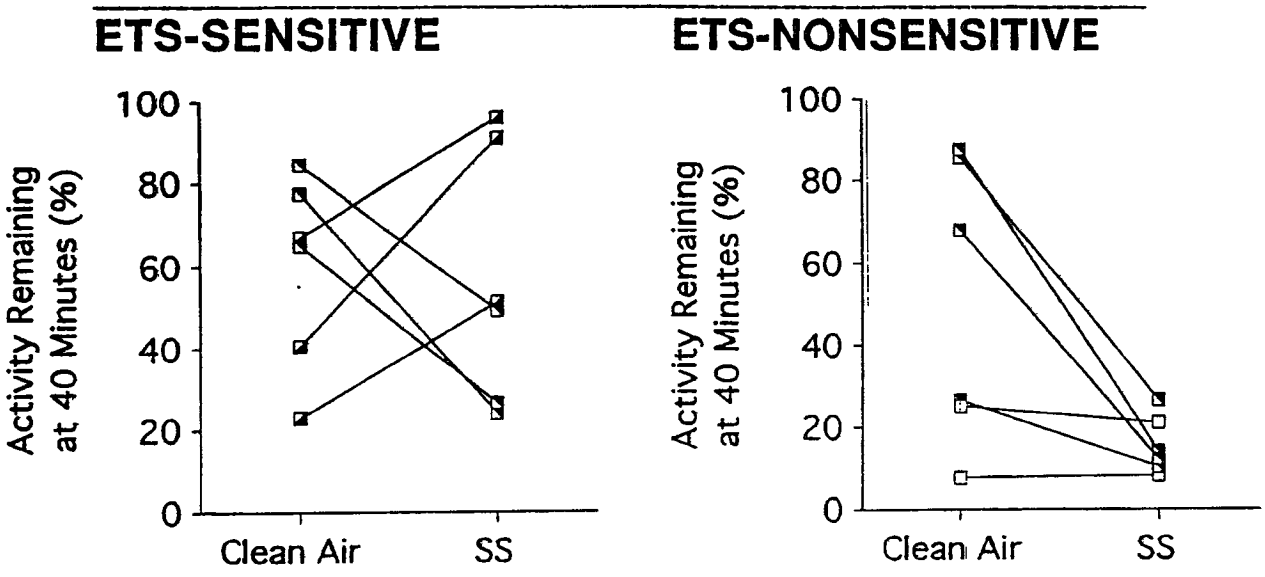

Figure: Individual subject results for total mucociliary clearance after controlled SS exposure. Shown is the activity remaining 40 minutes after administration of the ^{99m}Tc-sulfur colloid aerosol. Individuals were previously exposed to clean air or sidestream tobacco smoke (SS, 15 ppm CO, 1 hour).

Forty minutes after adminstration of the aerosol, a plateau in total clearance was observed, and at this time regional clearance was assessed. The spatial distribution of the tracer that remained in the nose 40 minutes after administration of the tracer was determined using a 5 x 1.5 cm collimator slit in with the long axis in a vertical orientation.

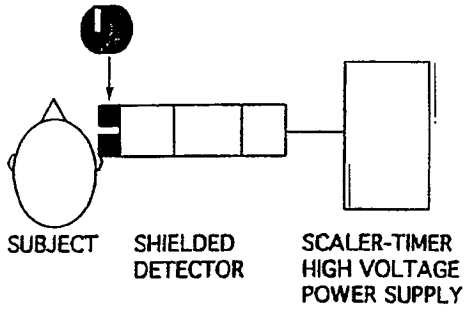

Figure: Apparatus for the detection of regional mucociliary clearance.

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The regions of the nose corresponding to the collimated slits are shown in the figure below:

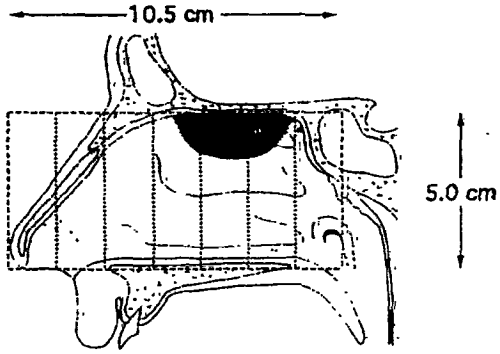

Figure: *Orientation of the collimated slits used for determination of regional mucociliary clearance.*

Results are shown below. The distribution of the tracer was similar under clear air conditions for both ETS-S and ETS-NS subjects. With SS exposure, ETS-NS subjects demonstrated increased clearance of tracer at all sites along the nose, but particularly in the anterior zone. In contrast, the ETS-S subjects showed persistence of the majority of the tracer in the anterior segments of the nose. There was a trend toward greater amounts of tracer in the most anterior 1.5 cm section of the nose.

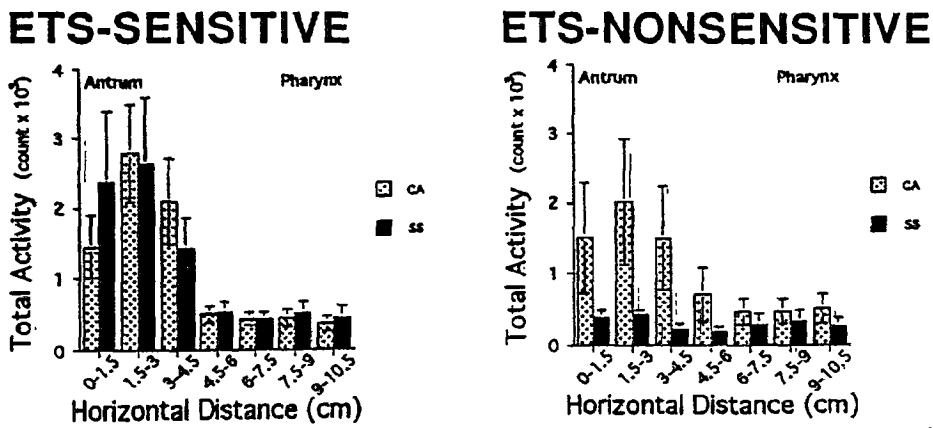

Figure: Activity remaining in the nose 40 minutes after the administration of a ^{99m}Tc-sulfur colloid in ETS-S and ETS-NS subjects. Subjects had previously been exposed to clean air (CA) or sidestream tobacco smoke (SS). See above for protocol.

Several aspects of these results are noteworthy. First, SS exposure, using this protocol, significantly accelerated mucociliary clearance in the ETS-S subjects. Half of the ETS-S subjects demonstrated a marked reduction in mucociliary clearance. These effects were

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demonstrable one hour after cessation of exposure to a moderate level of tobacco smoke. We are particularly interested in the ETS-S subjects that demonstrated persistent inhibited mucociliary clearance since this may be an early indication of increased susceptibility to exposure to this SS.

The prevailing wisdom regarding the effect of cigarette smoke on mucociliary clearance in the human nose has been that smoke does not alter nasal mucociliary clearance. This notion is based on a limited database[32, 33]. Studies by Frances et al[25] examined the effect of cigarette smoke on particle transport on the naso ciliary mucosa of donkeys. Whole cigarette smoke (either continuous injection of a 1:20 smoke:air mixture, or intermittent injection of a 40 ml bolus at 10 second intervals) produced no measurable effects on the transport rate of beads.

In contrast, a larger body of research indicates that tobacco smoke inhibits mucociliary transport in the tracheobronchial mucosa. Albert et al demonstrated inhibited tracheobronchial clearance after tobacco smoke exposure in a live unanesthetized donkey[34]. Other investigators have also demonstrated the inhibitory effect of smoke on tracheobronchial clearance in variety of animals including the cat, cow and rabbit[35-37]. Generally speaking, exposures were performed at concentrations intended to mimic mainstream tobacco smoke, thus much higher than levels consistent with environmental tobacco smoke exposure.

Cigarette smoke has been demonstrated in animal models or *in vitro* to affect distinct components of mucociliary clearance by one of several mechanisms, including altered viscoelasticity of the epiphase, decreased activity or loss of cilia, incoordinated or reversed direction of ciliary beating, and alteration of cell junctions[38]. Dehydration of the airway surface has been associated with reduced mucociliary clearance, and recent in vitro studies suggest that increased transepithelial fluid absorbtion may occur with tobacco smoke. Welsh et al demonstrated that cigarette smoke causes acute changes in ion transport across canine tracheal epithlium, thought due to a smoke-induced decrease in apical membrane chloride conductance. Jiang et al recently demonstrated that cigarette smoke increased fluid absorbtion across confluent monolayers of human nasal epithelial cells[39]. In their studies, transepithelial potential, resistance and solute-linked fluid transport were measured simultaneously. The monolayers absorbed fluid and this absorbtion could be inhibited by amiloride; in contrast ATP stimulated fluid secretion. Cigarette smoke increased fluid absorbtion, and the increase was not altered by amiloride. The authors concluded that cigarette smoke increased fluid absorbtion either by inhibiting secretion or by increasing amiloride-insensitve absorbtion. In the presence of smoke, the ATP or cAMP-induced fluid secretion was significantly reduced. The authors concluded that the cigarette smoke-induced increase in fluid absorbtion and the decreased secretory response to exogenous ATP and cAMP may play an important role in the pathophysiology of smoke related respiratory disease.

Our subjects that demonstrated inhibition of mucociliary clearance following smoke exposure may have been receiving an higher biologically effective dose of smoke, due to differences in baseline quantity of airway surface fluid. Alternatively the dose may have been the same, but a decreased organ reserve may be present, resulting in the inhibition of mucociliary clearance at a dose that accelerates clearance in other individuals. At present, we can only speculate on what aspect of mucociliary clearance is affected. It is possible that the ETS-S subjects have a higher rate of cigarette smoke-induced fluid absorbtion at the airway surface. We known from our lavage studies that ETS exposure in humans is unassociated with an increase in nasal fluid albumin, indicating that the quantity of airway surface fluid cannot be increased through increased vascular permeability and transudation of fluid and proteins. The airway surface may therefore be susceptible to dehydration from smoke exposure through a combination of increased fluid absorbtion and an absence of compensatory mechanisms for restoration of airway surface fluid. Alternatively, ciliary function could be directly, but

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differentially altered by smoke exposure[40]. Our proposal is to understand the effect of sidestream tobacco smoke on mucociliary clearance. If the differences observed in our preliminary studies prove to be reproducible, the mucosa of differentially sensitive individuals could be sampled and studied with in vitro smoke exposure. If local areas of the mucosa are identified that are particularly susceptible to the effects of smoke in vivo, these could be compared with more resistant areas of the mucosa. The accessibility of the nasal mucosa to biopsy or other methods of epithelial harvesting is one of the advantages of nasal research. A key initial step is to define the *in vivo* phenotype, through the studies outlined below.

III. JUSTIFICATION OF SPECIFIC AIMS AND HYPOTHESES:

The overall objective of this proposal is to further characterize the effect of sidestream tobacco smoke(SS) on mucociliary clearance in two subject groups: normal subjects with a history of upper respiratory sensitivity to environmental tobacco smoke (ETS-S), and normal subjects with no history of upper respiratory sensitivity to environmental tobacco smoke (ETS-NS). The **hypothesis** to be tested is that ETS-NS subjects will demonstrate acceleration of mucociliary clearance following controlled SS exposure, and that some ETS-S subjects will demonstrate a reproducible impairment of nasal mucociliary clearance after prolonged exposure to moderate levels of sidestream tobacco smoke with focal collection of tracer in the anterior 2-3 centimeters of the nose.

The initial experimental design consists of exposing subjects to SS and then assessing mucociliary clearance one hour after cessation of smoke exposure. This design was chosen for several reasons: 1)this was the design of our preliminary studies that showed the effects of interest, 2)effects that are persistent are more likely to cause adverse health consequences than those that are immediate but transient, 3)effects on mucociliary clearance have been shown by others to require one hour or more to develop[41], 4)ETS-sensitive subjects anecdotally report a lag in the development of some of their mucosal symptoms, although the acute congestion and irritation generally resolve within an hour.

AIM 1. To further characterize the effect of SS exposure on mucociliary clearance with respect to its spatial distribution and intrasubject reproducibility.

Our preliminary data indicate that ETS-NS subjects demonstrate an acceleration of nasal mucociliary clearance after SS exposure, while ETS-S subjects on average demonstrate no change in clearance. Half the ETS-S subjects demonstrated a significant reduction in clearance. Characterization of the spatial distribution of the mucociliary clearance will help us understand these results.

Our current scintillation detection system measures initial mucociliary clearance by positioning a single detector facing the subject("en face"), as sketched in the figure above(see Preliminary data). The scintillation detector records a signal that is inversely proportional to the square of the distance from the detector. Therefore, spatial information is lost in the aggregate measurement. We assume, based on preliminary work, that our aerosol delivery system results in uniform and consistent deposition of aerosol. However, our observations would be strengthened by direct assessment of the spatial characteristics of initial aerosol delivery in all subjects. With the new scintillation detection system that will be constructed with this grant, we will be able to determine the spatial characteristics of the initial aerosol deposition. Our **hypothesis** is that the ^{99m}Tc-sulfur colloid is deposited in a uniform manner in ETS-S and ETS-NS subjects. **Rationale:** In previous studies, nasal resistance and acoustic rhinometry measurements demonstrate similar nasal resistance and dimensional characterstics in the two groups one hour after smoke exposure. During the development of this technique, we

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demonstrated that our delivery system resulted in a uniform aerosol deposition when the delivery port was placed 0.2 cm anterior to the inferior turbinate.

Our current scintillation detector can be used to assess regional aerosol distribution, but at present this is done forty minutes after initial aerosol delivery, at a time when the aggregate clearance has plateaued(see preliminary data above). We are therefore unable to determine whether there are differences in the rate or direction of ^{99m}Tc-sulfur colloid clearance in different zones of the nose. Andersen used a single radioactive bead to demonstrate that clearance was slowest in the anterior and posterior one-quarter of the nose, and faster in the middle zone[19]. Proctor and others have postulated a zone in the anterior segment of the nose where mucociliary clearance is directed anteriorly (i.e. towards the nasal antrum)[7]. The size of this area, and its behavior under conditions of irritant exposure have not been delineated. Most investigators place their tracers posterior to this zone (i.e. in the middle region of the inferior turbinate).

Generally speaking, mucociliary clearance occurs in a single direction. However, some investigators have demonstrated that the direction of mucociliary clearance can be altered, at least in the tracheobronchial tree. Upko, working in Dr. Swift's laboratory, demonstrated both *in vivo* and *in vitro* that application of an electrical field to the dog trachea resulted in transient reversal of direction, then cessation of tracheal clearance[41]. In our interpretation of our data, we must consider the possibility of reversal of the direction of mucociliary clearance, as well as of alterations in the rate of clearance.

With the new scintillation detection system that will be constructed with this grant, we will be able to determine the spatial characteristics of the initial phase of the ^{99m}Tc-sulfur colloid clearance. The new detector will measure both en face, and four lateral, vertically oriented collimated zones simultaneously.

Our **hypothesis** is that ETS-NS subjects will demonstrate accelerated posterior clearance at all locations in the nose.

Our **hypothesis** is that the ETS-S subjects who demonstrate overall inhibition of clearance will demonstrate accelerated anterior-directed mucociliary clearance in the anterior 3 cm of the nose, and inhibition of posterior clearance in the remaining zones of the nose.

Rationale: Inspection of the regional clearance data(see preliminary data) indicates accelerated clearance throughout the nasal cavity in ETS-NS subjects. In contrast, ETS-S subjects had a tendency towards increased tracer in the anterior 1.5 cm of the nose. This is a zone that is anterior to the initial aerosol delivery, and suggests accelerated anterior-directed clearance. The new detector will allow these hypotheses to be tested directly.

The spatial characteristics of particle clearance in the anterior segment of the nose are not well understood. The anterior area of the nose is comprised of stratified squamous epithelium in the nasal antrum, changing to transitional epithelium, changing to pseudostratified columnar epithelium. The precise site of transition from squamous epithelium to transitional epithelium can be demonstrated by making a cast of the anterior nasal passage. Subjects lean forward and 2-4 ml of a rapidly-setting polymer is placed in the anterior nasal passage. The material that is used is Impramix® (vinyl polysiloxane), and it is used extensively for dental impressions. After setting in place in 5 minutes, a soft, readily removable cast has formed. The technique is well tolerated by subjects, and yields a soft but highly faithful cast with detailed surface features of the anterior nose. The zone of anterior particle clearance can be demonstrated by aerosolizing tantalum dust into the nose, and then creating a cast of the anterior nose one hour later. One of the striking features of a tantalum dust cast (created under clean air conditions) is that particles collect along a clearly defined line, 1-3 cm inside the nasal antrum. Using this method, we will be able to compare whether

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the site of particle collection in the most anterior zone of the nasal passage is the same or different in ETS-S and ETS-NS subjects.

We **hypothesize** that the site of particle accumulation under clean air conditions in the most anterior zone of the nose is similar for ETS-S and ETS-NS subjects. The reason for this is that total and regional clearance are similar for these two subject groups under clean air conditions.

A principal **hypothesis** of our proposal is that ETS-S subjects demonstrated marked increase in the retention of particles in the anterior segment of their nose following SS exposure. The tantalum dust-cast method will allow an independent testing of the hypothesis, and will allow verification of the conclusions from the ^{99m}Tc-sulfur colloid mucociliary clearance assay.

The final aspect of Aim 1 is to determine the reproducibility of changes in mucociliary clearance induced by tobacco smoke. Biologic variability in baseline mucociliary clearance among individuals is well-recognized[5]. Our preliminary data confirm this finding but also show marked variability in interindividual responsiveness to controlled SS exposure.

Our **hypothesis** is that individuals will demonstrate reproducible changes in mucociliary clearance following SS exposure. **Rationale:** Studies of acute responses to environmental pollutants are increasingly showing consistency in intra-individual responsiveness to pollutants, despite interindividual variability. The two best examples are McDonnell's data demonstrating the consistency of individual pulmonary function test decrements after ozone exposure in humans[42], and Kleeberger's data demonstrating consistent interstrain differences in neutrophil influx following ozone inhalation in inbred mice[43]. These data support the hypothesis that the host response to an irritant is determined by inherited factors, or by relatively stable acquired factors. Demonstration of the reproducibility of the effect is an essential first step before mechanistic studies can be initiated. If our subject's response to smoke is reproducible, and the spatial characteristics are defined, then *in vivo* mechanistic studies or *in vitro* mechanistic studies could be planned using nasal tissue obtained from these subjects. The inclusion of Dr. Yeates and Dr. Wong as consultants on this grant will ensure active discussion of these possibilities as data become available.

The data from aim 1 will be further analyzed to address the following questions: **a.** Is low baseline nasal mucociliary clearance predictive of smoke-induced inhibition of mucociliary clearance? **b.** Is low baseline nasal mucociliary clearance predictive of increased symptoms of upper respiratory irritation with controlled smoke exposure? **c.** Is a history of ETS-sensitivity predictive of increased risk of smoke-induced inhibition of mucociliary clearance? Questions **a** and **b** are hypotheses proposed by Andersen et al in the late 1970's(see Introduction above). Question **c** is our hypothesis, derived from our preliminary data.

AIM 2. To determine the exposure-response characteristics of altered mucociliary clearance in the upper respiratory tract following sidestream tobacco smoke exposure in ETS-sensitive and ETS-nonsensitive subjects, by determining the effects of exposure to clean air or SS at concentrations of 0, 1, 5, and 15 ppm CO on mucociliary clearance using the ^{99m}Tc-sulfur colloid clearance assay.

Other investigators have demonstrated that exposure to low level irritants typically accelerates mucociliary clearance, while exposure to higher levels of irritants inhibits mucociliary clearance. Our preliminary data shows that SS exposure (15 ppm, 1 hour) accelerates mucociliary clearance in ETS-NS subjects, but inhibits mucociliary clearance in a

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substantial number of ETS-S subjects. We interpret these results as suggesting that there has been a shift of the exposure-response curve for the ETS-S subjects.

The **hypothesis** is that the exposure-response is shifted to the left in ETS-S subjects.

Rationale: As noted in the introduction, the biphasic effect of irritants on mucociliary clearance can be broadly conceptualized in two ways. First, exposure to irritants initiates two competing sets of responses: those that accelerate and those that retard mucociliary clearance. The observed effect on muociliary clearance is the net effect of the two responses. If ETS-S subjects have lost the capacity to accelerate mucociliary clearance, then at lower concentrations of SS we will observe a continuing inhibition of mucociliary clearance, but of a lesser degree. An alternate concept is that accelerated mucociliary clearance is the normal compensatory response to irritant exposure, and that inhibition of mucociliary clearance only occurs when this compensatory reserve is exhausted. If this is true, then exposure of ETS-S subjects to lower concentrations of SS should result in a demonstration of accelerated mucociliary clearance with exposure to lower concentrations of SS. It is unknown whether the threshold for accelerated mucociliary clearance is the same or different in ETS-S and ETS-NS subjects.

AIM 3. To determine time-response characteristics of altered mucociliary clearance in the upper respiratory tract following sidestream tobacco smoke exposure in ETS-sensitive and ETS-nonsensitive subjects, by administering the ^{99m}Tc-sulfur colloid aerosol in advance of SS exposure, then exposing to smoke (15 ppm CO) with measurements using the scintillation detector after every 5 minutes of SS exposure.

Our preliminary data and AIMS 1 and 2 consist of assessment of mucociliary clearance one hour after cessation of exposure to SS. AIM 3 will seek to understand the initial moments of the mucociliary clearance response to SS. The ^{99m}Tc-sulfur colloid will be administered and a baseline mucociliary clearance profile established over ten minutes. Subjects will then begin smoke exposure, with repeat measurement of tracer distribution after every five minutes of smoke exposure.

Our **hypothesis** is that ETS-NS subjects will demonstrate a rapid onset of accelerated mucociliary clearance throughout the nasal cavity. ETS-S subjects will also demonstrate accelerated clearance initially, but clearance will cease as exposure continues.

Rationale: A full understanding of the comparative time-response characteristics of SS exposure and mucociliary clearance in these two subject groups will be a necessary step in developing mechanistic hypotheses to explain the observed physiologic differences between the two groups. At present we cannot predict when the differences in mucociliary clearance response will emerge, during or after smoke exposure. We favor the idea that ETS-S subjects have a present, but decreased reserve capacity to respond to irritants. They should therefore respond initially with accelerated mucociliary clearance to lower levels of SS. An alternative possibility is that both subject groups respond initially with inhibition of mucociliary clearance, but that ETS-NS subjects demonstrate a more rapid transition to a recovery phase, characterized by increased clearance.

AIM 4. To develop a convenient, objective way to assess mucociliary clearance in the upper respiratory tract, using an aerosol of a nonradioactive tracer coupled with nasal lavage.

Methods to assess nasal mucociliary clearance have been limited to the research laboratory because they generally involve the use of radioactive tracers, or require radiologic equipment to detect the passage of radioopaque probes. The saccharine test has been used in some field studies but has important limitations: the endpoint requires the subject's perception of a

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sweet taste on the back of the tongue, and the tracer placement is in a small region of the nose. Many patients with indoor air complaints report distortion of taste sensation, but the saccharine test presumes uniform taste between subjects. Animal studies demonstrate that effects of irritants on the nasal mucosa are located in different segments of the nose, but the saccharine test covers only a narrow trajectory in the nose, with placement of the tracer distal to one of the most vulnerable regions.

The Center for Indoor Air Research is interested in developing methods that are applicable for field studies. The purpose of the field studies will be to assess long term health effects in environments where exposure to complex mixtures occur. According to the National Research Council Report on Biologic Markers in Pulmonary Toxicology, methods for measurement of mucociliary clearance "examine an important set of defense mechanisms of the respiratory system, and alterations of the mechanisms sometimes give an early indication of an adverse impact of inhaled environmental agents"[5].

Fluorescent probes have been used in clinical medicine and clinical research for many years, particularly by ophthamologists. Fluorescein is injected intravenously to visualize retinal blood vessels, and is instilled into corneal fluid to seek evidence for corneal erosion during a slit lamp examination. The extensive experience with these probes indicates their safety for use in humans. Fluorescent probes are stable and have slow rates of decay. Thus, unlike the short acting radioactive tracers used in the laboratory, samples containing these tracers can be collected in the field, and transported to the laboratory for analysis. A possible limitation is that exposure to light can cause decay of the tracer. However, storage in amber vials or in a sealed box can readily overcome this limitation. Fluorometers are also available for field use.

Fluorescent probes have been used by Dr. Swift for the generation, characterization, and quantitation of aerosols. Fluorescent aerosols can be collected in a Cascade impactor, and the quantity of an aerosol in a particular size range can be determined with a fluorometer. The sensitivity of the fluiorometer is a further advantage of this type of tracer.

Recevery of fluid from the nasal cavity can be performed in several ways. Nasal lavage is traditionally performed by have subjects extend their neck, close their palate, and instilling 3-7 ml of warmed saline into the nose with a pipette. After ten seconds, subjects flex their neck and expel the lavage fluid into a basin for recovery and processing. A second method, developed by Dr. Michael Kaliner, consists of placing catheters in the floor of the nasal cavity, and spraying aliquots of saline into the nose while aspirating from the catheters. A third method is described under Experimental Methods. We hypothesize that a nonradioactive, fluorescent-based assay can be developed that is simple, reproducible, readily tolerated by subjects, and appropriate for field studies.

The proposed research is entirely feasible since it draws on established expertise of Drs. Bascom and Swift. The investigators have demonstrated that they have access to appropriate subjects, can perform controlled challenge studies with sidestream tobacco smoke, and assess mucociliary clearance.

B. Qualifications of Investigator

Rebecca Bascom M.D. M.P.H.is an established investigator, experienced in the design and conduct of controlled human exposure studies and the assessment of physiologic and inflammatory responses in the upper and lower respiratory tract. She is board certified in internal medicine/pulmonary disease, preventive/occupational medicine and completed research training in clinical immunology. Her research has focused on allergic and irritant responses of the upper respiratory tract, and the basis for sensitivity to irritants. Since

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1986, she has been director of the Environmental Research Facility at the University of Maryalnd. The facility is a human exposure chamber which performs human air pollution studies. Current projects primarily focus on characterization of sensitivity to sidestream tobacco smoke, and on determining the effects of ozone on the upper respiratory tract.

David Swift, Ph.D. is an established investigator, experienced in studies of the physiologic responses of the upper respiratory tract, and in the generation and monitoring of aerosols. He is professor in the Division of Environmental Health Engineering (Johns Hopkins School of Hygiene and Publich Health), and has a lifelong interest in aerosol physics and the modeling and measurement of the dose, distribution and clearance of aerosols in the human upper respiratory tract. He has published studies measuring mucociliary clearance in the upper respiratory tract.

Drs. Swift and Bascom have collaborated together over the past ten years, most recently through a Center for Indoor Air Research grant entitled "Environmental Tobacco Smoke: Nasal Response and Aerosol Deposition Effect." (10/1/90-9/30/93) The current proposal has been developed as a result of findings from collaborative work performed at both institutions over the past two and one half years.

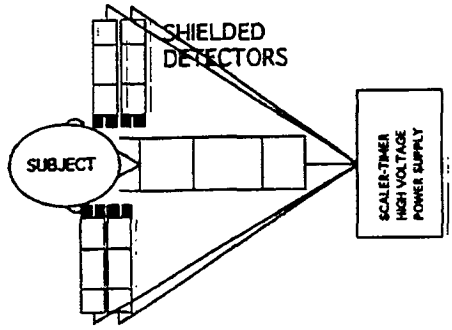
9. EXPERIMENTAL PLAN

A. DESIGN

Figures in the appendix show study protocols in schematic fashion.

AIM 1. To further characterize the effect of SS exposure on mucociliary clearance with respect to its spatial distribution and intrasubject reproducibility

The scintillation detector will be redesigned to permit simultaneous en face and collimated measurements with a lateral projection. These detectors, operating simultaneously, will record the location of the tracer at 2 minute intervals.



Eight ETS-sensitive and eight ETS-nonsensitive subjects will participate in this study. Each subject will be studied on three separate days, each study date separated by at least two weeks. Each subject will record baseline symptoms during a one hour equilibration period. The subject will then be exposed for one hour at rest to clean air or SS at a carbon monoxide concentration of 15 parts per million. The SS exposure will occur in duplicate, on two separate days. Symptoms will be recorded at intervals during the exposure period. Subjects will exit the chamber and remain in a clean air environment for one hour. One hour after the cessation of

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SS exposure, an aerosol of ^{99m}Tc sulfur colloid will be administered to one nostril, and an aerosol of tantalum dust will be administered to the contralateral nostril. Measurements of the ^{99m}Tc-sulfur colloid clearance wil be performed with a scintiallation detector at 2 minute intervals, with 30 seconds required for each reading. One hour after administration of the tracers, 2-4 ml of Impramix® will be placed in the anterior segment of the nasal passage on the side that received the tantalum dust. After five minutes, the polymer will be removed and inspected for the distribution of the dust. The results of the ^{99m}Tc-sulfur colloid mucociliary clearance assay will be compared with the independent assessment of particle clearance using the tantalum dust and Impramix® impression of the anterior segment of the nose. The reproducibility of the mucociliary clearance response to tobacco smoke within subjects will be determined by comparing the intraindividual variability of the response to SS on two SS exposure days, separated by at least 2 weeks.

AIM 2. To determine the exposure-response characteristics of altered mucociliary clearance in the upper respiratory tract following sidestream tobacco smoke exposure in ETS-sensitive and ETS-nonsensitive subjects.

Eight ETS-S and eight ETS-NS subjects will be studied. The ETS-S subjects will have been shown in previous studies, or in a screening study, to have inhibition of mucociliary clearance with SS exposure. The ETS-S subjects will have been shown in previous studies, or in a screening study, to have acceleration of mucociliary clearance. These selection criteria will be reviewed based on the results from AIM 1. Each subjects will be studied on four study days, each day separated by at least two weeks. Subjects will record baseline symptoms and undergo controlled exposure at rest for one hour to clean air or sidestream tobacco smoke at a concentration of 1, 5, or 15 ppm CO. One hour after cessation of smoke exposure, subjects will undergo assessment of mucociliary clearance using the ^{99m}Tc-sulfur colloid assay.

AIM 3. To determine the time-response characteristics of altered mucociliary clearance in the upper respiratory tract following sidestream tobacco smoke exposure in ETS-sensitive and ETS-nonsensitive subjects

Eight ETS-sensitive and eight ETS-nonsensitive subjects will be studied. The ETS-sensitive subjects will have been shown to have an inhibition of mucociliary clearance with controlled SS exposure. The ETS-nonsensitive subjects will have been shown to have accelerated mucociliary clearance with controlled SS exposure. Subjects will record symtpoms and undergo equilibration for one hour. The ^{99m}Tc-sulfur colloid will be administered and clearance measured for ten minutes. Subjects will enter the chamber and begin exposure to SS (15 ppm CO, 1 hour), exiting the chamber briefly every five minutes for measurement of mucociliary clearance. The measurements will not be made in the chamber because the smoke would soil and perhaps alter the performance of the detector system. The selection criteria and exposure plans will be reviewed based on the findings from AIMS 1 and 2.

AIM 4. To develop a simple, convenient, and objective method, suitable for field studies, to assess mucociliary clearance in the upper respiratory tract.

The components of the assay will be administration of an aerosol of a nonradioactive tracer, followed by nasal lavage to recover remaining tracer, and analysis of the lavage fluid to quantify the presence of the tracer. The goal is to develop an assay that will require 45 minutes or less of a subject's time. The assay will be characterized with respect to its coefficient of variation for repeated measures, and its consistency over time in a group of ETS-sensitive and ETS- nonsensitive subjects. The technique will be validated using the radiolabelled method, and

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the technique characterized with respect to inter and intrasubject variability in anticipation of its applicability to field studies. Additional details about the fluorescent method are outlined below.

B. METHODS

Subject selection and characterization

Healthy nonsmoking young adults (ages 18-45) are recruited by advertising at a professional urban campus (University of Maryland at Baltimore). Subjects complete a health history questionnaire and those with chronic cardiorespiratory conditions are excluded from the study. A screening questionnaire asks subjects to rate their history and severity of symptoms associated with exposure to environmental tobacco smoke on a 0-5 scale (0=no history of symptoms, 1=mild symptoms, 3=moderate symptoms, 5=severe symptoms). Symptoms of eye, nose, throat irritation and headache that occurred with historical ETS-exposure are summed to calculate a "historical ETS-irritation index" and symptoms of nasal congestion, rhinorrhea, sneezing and post-nasal drip that occurred with historical ETS-exposure are summed to calculate a "historical ETS-rhinitis index". Subjects with an ETS-rhinitis index of ≤ 1 are termed "ETS-nonsensitive", while subjects with an index of >2 are termed "ETS sensitive".

Subject undergo a screening challenge with sidestream tobacco smoke (STS) (15 ppm CO, 1 hour) at rest. Those with a greater than 50% increase in nasal resistance are termed "ETS-responsive" while those with a smaller increase are termed "ETS-nonresponsive". ETS-responsiveness will not be used as a selection criteria. However, it will remain part of subject characterization in order to understand the relationship between congestive responses and altered mucociliary clearance.

Subjects undergo a battery of prick skin tests to common allergens, and atopy is defined as the presence of one or more positive skin tests. A positive skin test is defined as being greater than 1/2 the histamine diameter.

Sidestream tobacco smoke(SS) exposure

Subjects will be studied at the University of Maryland Envrionmental Research Facility. A diagrams of the exposure facility is appended. Outcome measures are performed in a 41 m^3 clean room and exposures are performed in a 22 m^3 exposure room. Intake air for both rooms is filtered by HEPA filters and activated carbon filters, and conditioned to constant temperature and humidity (71°C, 42% R.H.)

Sidestream tobacco smoke (SS) is generated with a 4.4 ft^3 automated smoking machine, designed by L. Sauder, built by the Department of Engineering, University of Maryaldn, College Park, and modified in consultation with Roger Jenkins Ph.D. (OakRidge National Laboratories, consultant, Center for Indoor Air Research). Standard 1R4F cigarettes (Tobacco and Health Institute, Lexington, Kentucky) are preconditioned for 24 hours at 23.8°C, 60% R.H.. One, five, or fifteen cigarettes are burned simultaneously to generate SS at concentrations of 1, 5, and 15 ppm CO, respectively. Cigarettes are burned using a standard puff profile (puff duration 2 seconds every minute, puff volume 35 ml achieved with 13.7 cm vacuum pressure). Cigarettes are positioned horizontally in a manifold connected to a timing device. Mainstream tobacco smoke is exhausted to the outside with a vacuum system. SS is delivered to the exposure room through a ceiling diffuser and exits the exposure room without recirculation. The ventilation rate in the exposure rooms enables 9 air changes per hour.

Cigarette smoke concentrations are monitored using two real-time carbon monoxide analyzers (Ecolyzer 2000 Series CO Meter, Energetics Science, Pittsburgh, PA; Bendix Model 8501-5CA Infrared Gas Analyzer, Lewisburg, WV). Total volatile organic compounds (HNU PI

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101 Trace Gas Analyzer, Newton MA) are measured using isobutylene as the reference standard. Particles are enumerated with a Climet Model 226 High Resolution Airborne Particle Analyzer/Model 8040 Continuous Monitor (Climet Instruments, Redlands, CA). For particle analysis, the airstream is diluted 1:224 to avoid coincidence of particles. Nicotine concentrations are determined by collecting 60 liter air samples in XAD-4 sorbent tubes (SKC, Eighty Four PA) with an SKC Universal Constant-Flow Air Sample Pump Computer-Controlled Deluxe Model 224-PCXR7 and analyzed using gas chromatography-mass spectroscopy with a phosphorus-nitrogen detector (Maryland Spectral Services, Baltimore, Maryland) (Ogden 1989).

Mucociliary clearance: Mucociliary clearance is determined using an aerosol of ^{99m}Tc-sulfur colloid(Syncor Corporation, Timonium MD). This isotope has a short half-life ($t_{1/2}$ = 6 hours) and the dose is only 10 mrem to the nasal passage each time a subject is studied. The low radiation dose is possible because of the sensitivity of the scintillation detector. The aerosol(1 ml of 5 mCi/ml ^{99m}Tc-sulfur colloid in saline) is delivered to the nasal passage using a deVilbus No. 40 nebulizer (particle size range 2-8μm). The aerosol generator is attached to a thin tube that is positioned in the nasal passage 0.2 cm anterior to the anterior border of the inferior turbinate. Preliminary studies indicated that this site resulted in uniform deposition and clearance rates. The detector system consists of a sodium iodide thallium crystal shielded scintillation detector coupled with to a scaler-timer and high voltage power supply. The detectors will be linked to a computer for automated data acquisition and transfer to spreadsheet for data analysis. The components of the system include ORTEC Components: Bias Supply 0-2 kv (#478), Ratemeter counts/sec (#661), Preamplifier-amplifier (#4890), Dual counter/timer (#994), Internal power supply 6V (#99X-4), Minibin Power supply (#4001M). Detectors are supplied by Bicron (#3XM.5Q/3AL). The aerosol is administered to achieve an initial signal of 10,000 cpm/30 seconds against a background of 250 cpm/30 seconds. Subjects are positioned using a sculpted facepiece with alignment of marks on the facepiece and the subject's face. The tip of the nose, entrance to the nasal antrum, and ear are used as reference points for placement of the collimated slits. The diameter of the en face scintillation detector is 7 cm and the slit size for the lateral detectors will be 1.5 x 5 cm with the long aspect of the slit placed in a vertical position. Lateral detectors will be positioned on alternate sides of the face, moving posteriorly. Counts will be performed at 2-5 minute intervals, depending of the specific protocol. Percent clearance at 40 minutes will be used as the initial, primary descriptor. Clearance data will be inspected and analyzed for evidence of anterior particle clearance (net increase in the most anterior zone), and focal accumulation of tracer.

Tantalum dust-vinyl polysiloxane impression: Tantalum dust will be aerosolized into the anterior portion of the nasal passage. One hour later, an impression will be made of the anterior nasal passage. Impramix®(Rugby Labs, Rockville Centre, NY), is a vinyl polysiloxane polymer used routinely for dental impressions. Two to four ml are placed in the anterior nasal passage (the consistency of toothpaste, changing to the consistency of putty) and left in place for five minutes. Upon removal, particles present in the nose and surface characterisitics are faithfully retained.

Non-radioactive assessment of mucociliary clearance: Nasal lavage of a non-radioactive fluorescent tracer will be used to determine temporal and spatial characteristics of mucociliary clearance in the nasal passage of ETS-S and ETS-NS subjects. We propose to develop, test and employ a method for field measurement of nasal mucociliary clearance which is relatively simple and does not require a radioactive substance. The candidate substance which we believe has a high probability of meeting these criteria is fluorescein in its non water soluble form(Janssen Chimica, available through Spectrum Chemical Mfg Co.). The water soluble form of fluorescein, also known as uranine, is not suitable for this measurement because its solubility in the saline layer of the nasal epithelial liquid secretion (where mucociliary clearance takes place) is likely to lead to transport across the epithelium and uptake into the circulation or the epithelial cells.

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The proposed method consists of spraying a saline suspension of the nonsoluble fluorescein (henceforth called fluorescein) particles onto the nasal mucosa just posterior to the nasal valve, about 2 cm posterior to the nostril. After a suitable period for clearance to occur(usually 20 minutes), the remaining particles are removed in suspension by a saline lavage of the nasal passage. This lavage is proposed to be carried out in a specified fashion, employing a given volume of saline wash (in a syringe) which is introduced into the nasal passage at the nostril. In this proposed lavage method, the subject's head is tipped downward so that the axis of the main nasal passage is vertical (this passage is horizontal in the normal upright position). A water-tight seal is maintained where the syringe enters the nostril so that the lavage fluid enters the anterior nasal region and fills posteriorly to the chosen volume. In this fashion, successively greater lavage volumes can be serially introduced into the nasal passage to remove progressively more posterior located particles. By this means, the spatial distribution of the cleared particles which remain in the nasal passage can be readily determined.

If it is desired to determine the percent clearance after a given time period, without reference to the spatial distribution, the traditional nasal lavage technique can be used to wash out all the fluorescein in the nasal passage, with on a single side (anterior to the end of the septum) or on both sides (to the posterior wass of the nasopharynx). Particles which have been cleared to the latter position are removed by swallow and are counted as being totally cleared.

After the particles are lavaged from the nasal passage in the saline lavage, they are filtered from the saline suspension and dissolved in ethyl alcohol for concentration analysis using a standard, highly sensitive fluorometer (Model 10-AU-000 Laboratory Fluorometer, Turner Designs, Sunnyvale, CA), limit of detection 10 parts per trilllion of rhodamine WT in water. Dr. Swift has been using a fluorescein-based system using this fluorometer for the generation and measurement of aerosols using a Cascade impactor for size detection.

C. ANALYSIS OF DATA

Statistical analysis of the data will be performed by Dr. Thomas Permutt, a biostatistician in the Department of Epidemiology and Biostatistics and The University of Maryland School of Medicine. Dr. Permutt is familiar with the design and conduct of human challenge studies and has collaborated with the Environmental Research Facility for the past three years.

1. To further characterize the effect of SS exposure on mucociliary clearance with respect to its spatial distribution and intrasubject reproducibility

Total mucociliary clearance will be expressed as the percent tracer remaining, using the initial reading as 100%. This measurement will be taken from the en face scintillation detector. Analysis of variance will be performed within and between groups of subjects (clean air vs. SS as the within subject factor and ETS-S vs. ETS-NS as the between subject factor). Individual subject results will be displayed for the reading at 40 minutes post tracer administration.

Uniformity of the delivery of tracer will be determined by calculating the proportion of ^{99m}Tc-sulfur colloid tracer that is recorded at each of the four lateral collimation slits. Variation of less than 10% in the initial delivery pattern will be considered as evidence of uniform initial deposition pattern. Patterns of tracer clearance will be determined by normalizing the values of the lateral collimation slits to the initial reading ("baseline"). A % baseline value will be calcuated for all time points.

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Evidence for anterior-directed clearance of tracer will be sought by analyzing the change in the quantity of tracer detected by the most anterior slit.

Baseline mucociliary clearance, smoke-induced symptom scores and smoke-induced alterations in mucociliary clearance will be correlated by linear regression analysis.

Intrinsic host factors that predict inhibition of mucociliary clearance will be sought. Screening nasal airway resistance, acoustic tracings, symptom scores, atopic status and baseline mucociliary clearance will be compared for ETS-sensitive and ETS-nonsensitive subjects and for subjects who do and do not demonstrate inhibition of mucociliary clearance with SS exposure.

The tantalum dust-vinyl polysiloxane cast will be inspected and the demarcation line of particle clearance will be measured. The casts of ETS-S and ETS-NS subjects will be compared for qualitative and quantitative differences in the distribution of tantalum under clean air and SS conditions.

The reproducibility of the response to SS exposure will be quantified by correlating the symptomatic and clearance response of individual subjects on the two SS study days using linear regression analysis.

2. To determine the exposure-response characteristics of altered mucociliary clearance in the upper respiratory tract following SS exposure.

The total and regional clearance will be quantified as outlined in AIM #1. Exposure-response curves will be drawn for the two study groups and inspected. The percent tracer remaining at 40 minutes will be compared for the four exposure conditions using analysis of variance with Dunnette's test for comparison of individual values.

3. To determine the time-response characteristics of the response to SS.

Total and regional clearance will be quantified as outlined in AIM #1. Individual subject and aggregate data will be inspected for patterns of accelerated or inhibited mucociliary clearance. Percent tracer remaining will be compared using analysis of variance with Dunnette's test for comparison of individual values.

4. To develop a convenient method, appropriate for use in field studies, to assess mucociliary clearance in the upper respiratory tract.

The effect of three different methods of nasal lavage on the mucociliary clearance results will be described. The effect of different quantities of nasal lavage fluid on the return of the tracer will be described.

The fluorescent mucociliary clearance assay will be described by calculated a coefficient of variation for repeated measures performed under clean air conditions in a group of ETS-S and ETS-NS subjects.

The correlation with the ^{99m}Tc-sulfur colloid assay will be performed by linear regression analysis of clearance determined at comparable time points after administration of the tracer.

D. INTERPRETATION OF RESULTS

The interpretation of the results of our studies will be influenced by the following considerations:

Reproducibility: If our data indicate that SS-induced effects on nasal mucociliary clearance show intraindividual reproducibility, we will conclude that this response to SS indicates a host factor that is stable over the time period studied. The "host factor" may be determined by one or more of the following factors: genetic background, previous toxic exposures, the presence of

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disease (e.g. allergy), the presence of sub-clinical inflammation or other alteration in mucosal function(cause unknown).

Sensitivity: Our preliminary data suggest that smoke-induced inhibition of mucociliary clearance will not be a sensitive biomarker of subjective sensitivity to ETS exposure. Only half of the ETS-S subjects demonstrated inhibition of mucociliary clearance after SS exposure.

Specificity: Our preliminary data suggest that smoke-induced inhibition of mucociliary clearance may be a specific biomarker of subjective sensitivity to ETS exposure. None of the ETS-NS subjects demonstrated inhibition of mucociliary clearance after SS exposure.

Applicability: We will consider tests of the effect of smoke on nasal mucociliary clearance to be an applicable biomarker of upper respiratory tract mucosal function.

Generalizability: The effects of SS on nasal mucociliary clearance that we show will be specific to the experimental conditions of the study. It will be inappropriate to perform population estimates based on our data, since the subjects are carefully selected and do not represent a cross-section of the general population. If effects on nasal mucociliary clearance are demonstrated only at SS exposures of 15 ppm CO, then the relevance of our findings as an index of a direct SS-induced health effect would be limited, since ETS exposures are typically lower in indoor environments. The potential utility of SS-induced effects of nasal mucociliary clearance as a biomarker of susceptibility would remain, however.

Limitations: One of the criticisms of mucociliary clearance assays are that they represent the aggregate of multiple functions at the airway surface including ciliary function (beat frequency, beat strength, coordination of beats), airway surface fluid quantity and composition (determined by ion flux, protein and water transport) and the physical properties of mucous(viscoelastic properties). This so-called limitation is, in fact, a strength. Mucociliary clearance is an aggregate function, and therefore is a good candidate for a biomarker. Clearly, assessment of changes in mucociliary clearance do not allow for a determination for the mechanisms by which the changes occur. At present, techniques to assess ciliary beat frequency in vivo are limited to studies in anesthetized animals, using rigid bronchoscopes. It is anticipated that methods will be developed by Dr. Wong within the next several years to measure ciliary beat frequency in the human nose *in vivo*. The careful characterization of the exposure-response and time-response relationshps planned in this study will significantly advance our ability to plan mechanistic studies in the future.

Future Directions: If acute SS-induced changes of nasal mucociliary clearance are reproducible, then we will design studies to establish the mechanism of the differential responsiveness, in collaboration with Drs. Yeates and Wong. If we are able to establish acute SS-induced inhibition of nasal mucociliary clearance as a specific biomarker of ETS-sensitivity, then we suggest studies be performed to determine whether this is a biomarker of susceptibility to other environmental exposures, both in controlled human studies and in field studies. In field studies, the study design would be as follows: subjects would be initially characterized with respect to the "inhibitability of nasal mucociliary clearance", then followed longitudinally to determine whether this host characteristic is predictive of adverse health outcomes, including symptoms, acute respiratory illness, and chronic respiratory symptoms. Finally, subject groups that may be at increased risk of adverse effects from environmental exposures could be investigated. These include subjects with allergic rhinitis, those with recent viral infections, or subjects with an illness behavior related to VOC exposure, such as multiple chemical sensitivity-type syndromes.

E. TIMETABLE FOR THE INVESTIGATION

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Year 1: Aim 1

Year 2: Aim 2, begin Aim 4

Year 3: Aim 3, complete Aim 4

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10. AVAILABLE FACILITIES AND RESOURCES

Laboratory: The University of Maryland Environmental Research Facility has conducted major controlled human studies over the past twenty years on the health effects of criteria outdoor air pollutants (ozone, sulfur dioxide, particles) and indoor pollutants (environmental tobacco, smoke, formaldehyde). Projects have been funded by the National Institutes of Health, Center for Indoor Air Research, The Health Effects Institute, the Department of Energy and the Environmental Protection Agency. The Environmental Research Facility consists of 3000 ft^2 of contiguous space including a two room Environmental Chamber, laboratory space for pollutant generation and monitoring laboratory space for rudimentary sample processing, an examination room, a bronchoscopy room, pulmonary function testing and exercise testing room, as well as office support space, a conference area and a reception area. The Facility is equipped to perform and process nasal scrapings, nasal lavages, nasal disc samples and to perform posterior rhinomanometry and acoustic rhinometry. The capability to measure mucociliary clearance is being moved from Dr. Swift's Laboratory to the Environmental Research Facility. Dr. Bascom is Director of the Environmental Research Facility and hence access to the facility for this project is assured. The Staff of the Facility meets each week to review the status of current and future projects. Collaborators attend the meetings as appropriate (see specifics for this project below). The technical staff of the Facility is experienced in the procedures proposed for the study, and in the requirements for subject recruitment and retention during extended studies.

Animal: Not applicable

Computer: Computer resources include 3 IBM-compatible computers which are part of the pollutant monitoring system and rhinometry systems at the Environmental Research Facility. IBM and Macintosh PCs are in the office of or readily available to all Core participants and are currently used for data reduction, word processing, and manuscript preparation. Modems connect computers to medical reference databases (e.g. Grateful Med). There is an IBM 4301 at the information resources and Management Division, University of Maryland School of Medicine which is used for analysis of large data sets. Dr. Permutt performs statistical analyses using the SASS system on an IBM compatible computer. Preparation of manuscripts will be facilitated by purchase of a laptop computer for Dr. Bascom.

Office: Office space is provided for both the principal investigator and support personnel in the Environmental Research Facility and at the MSTF Building, located one block from the Environmental Research Facility.

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Other:

The laboratory of Dr. David Swift will be the site of the construction and initial testing of the improved scintillation detector that will be constructed for this study. His laboratory will also perform the development and initial testing of the fluorescent tracer-based mucociliary assay (Alan 4). Dr. Swift's laboratory is located at the Johns Hopkins School of Hygiene and Public Health, which is also located in downtown Baltimore approximately fifteen minutes from the Environmental Research Facility. Dr. Swift is a co-investigator on the project and facilities will be available as needed by the project. Dr. Bascom and Dr. Swift are currently co-investigators on a grant investigating the effects of sidestream tobacco smoke on mucociliary clearance. The coordination of these investigators and their teams is well-established. Dr. Swift and Dr. Bascom meet monthly to review the status of current projects. Additional working sessions in the laboratory are scheduled as needed to develop methodology.

Dr. Thomas Permutt will consult in the study design and analysis. He is biostatistician in the Department of Epidemiology and Preventive Medicine. Dr. Permutt attends meetings of the Environmental Research Facility once a month to discuss current and future projects. Dr. Permutt's office is located one block from the Environmental Research Facility.

MAJOR EQUIPMENT

University of Maryland Environmental Research Facility:
- Environmental Chamber (see attached diagram)
- Exercise bicycle
- Metabolic cart to measure minute ventilation
- Sidestream Tobacco Smoke Generation System
- Climet Model CI 226-210 Particle Analyzer; TSI Model 3030 Electrical Aerosol Analyzer
- Beckman Carbon Monoxide Analyzer
- HNU Total Organic Vapor Meter Model 101
- Posterior Rhinomanometry with automated analytical software.
- Acoustic Rhinometry

Dr. David Swift's Laboratory
- Scintillation detector system for measurement of total and regional nasal clearance
- Aerosol generator systems (e.g. condensation generator, spinning disc generator, jet and ultrasonic nebulizers
- Aerosol characterization instruments (e.g. cascade impactor, light scattering, aerosol spectrometer, aerodynamic particle spacer, condensation nuclei counter)
- Aerosol delivery system for human exposure
- Flow-pressure and velocity measuring instruments
- Radioaerosol and fluorometric instruments
- Acoustic rhinometer

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11. OTHER SUPPORT

CURRENT ACTIVE SUPPORT - Rebecca Bascom, M.D.

a. Source and identifying no. National Heart, Lung and Blood Institute R 29 HL 40945 P.I. Rebecca Bascom, M.D.
Title: Respiratory Sensitivity to Environmental Tobacco Smoke
b. Your role on the project: P.I. Effort 50%
c. Dates and costs of entire project: 04/01/89 - 03/31/94; $350,000 (direct cost)
d. Dates and costs of current year: 04/01/93 03-31-94; $74,133 (direct cost)
e. Specific aims of project: The aims of this project are: 1) To characterize the symptomatic, physiologic and inflammatory response to sidestream tobacco smoke (STS) in the environmental tobacco smoke (ETS) sensitive subjects and to determine whether the organic phase component of ETS is responsible for ETS sensitivity. 2.) To characterize the dose-response to STS in ETS sensitive individuals, 3.) To characterize the pharmacology to ETS sensitivity, 4.) To characterize the lower respiratory response to STS in ETS sensitive subjects under conditions of moderate exercise and 5.) To determine the effect of exposure to antigen on the response to STS in ETS sensitive allergic subjects.
f. Describe scientific and budgetary overlap: There is no scientific and/or budgetary overlap with this application.
g. Describe adjustments you will make if the present application is funded (budget % effort, aims, etc.) No modifications will be necessary should this application be funded.

a.) Center for Indoor Air Research, 90-30, "Environmental Tobacco Smoke: Nasal Response and Aerosol Deposition Effect. Active.
b.) P.I.: 25% effort
c.) 10/01/90 - 9/30/93; $377,891 (direct cost)
d.) 10/01/92 - 9/30/93; $127,662 (direct cost)
e.) The aims of this project are: 1) To determine the anatomic location of the physiologic response to controlled challenge with sidestream tobacco smoke (STS) in the upper respiratory tract using the technique of acoustic rhinometry. 2) To determine the effects of STS exposure on the distribution and fate of secondary particulate pollutants in the respiratory tract 3) To determine the efficacy of commercially available room air cleaners in reducing the response to STS in sensitive subjects.
f.) There is no scientific and/or budgetary overlap with this application.
g.) No modifications will be necessary should this application be funded.

PENDING SUPPORT - Rebecca Bascom, M.D.
NONE

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Source: https://www.industrydocuments.ucsf.edu/docs/rxnm0000

CURRENT ACTIVE SUPPORT - David Swift, Ph.D.

Name David L. Swift Active

a. Source and identifying no. U.S. Dept. of Energy DE-FGOZ-88ER 60655 PI David L. Swift
Title: Regional Aerosol Deposition n Human Upper Airways
b. Your role on project P.I. Effort 40
c. Dates and costs of entire project: 6/1/88 - 2/28/94
d. Dates and costs of current year: 3/1/92 -2/28/93; $63,636
e. Specific aims of project: Study of the behavior of aerosol particles in the human nasal and oral passage, with special emphasis on radon progeny size aerosols (I um - 0.5 um)
f. Describe scientific and budgetary overlap: None
g. Describe adjustments you will make if the present application is funded (budget% effort, aims, etc.) None

a. NIOSH 0h07090 P.I.: M. Corn
"Occupational Health Resources Center; Industrial Hygiene and Safety Program" Active
b. Director of one core (1H&5) of the center; 10% effort
c. 7/01/92 - 06/30/97; $3,000,000 (Total center)
d. 07\01\92 - 06/30/93; $136,000
e. Training grant for masters and doctoral students in industrial hygiene and safety; support for teaching faculty and students.
f. None.
g. None; no overlap

a. University of Maryland P.O. 786276 Active. P.I.: Rebecca Bascom, M.D. "Environmental Tobacco Smoke: Nasal Response and Aerosol Deposition Effect"
b. Investigator; 15% effort
c. 10/01/90 - 09-30/93; $120,277
d. 10/01/92 - 09/30/93; $ 38,634
e. The aims of this project are: 1) To determine the anatomic location of the physiologic response to controlled challenge with sidestream tobacco smoke (STS) in the upper respiratory tract using the technique of acoustic rhinometry. 2) To determine the effects of STS exposure on the distribution and fate of secondary particulate pollutants in the respiratory tract 3) To determine the efficacy of commercially available room air cleaners in reducing the response to STS in sensitive subjects.
f. None.
g. None.

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Source: https://www.industrydocuments.ucsf.edu/docs/rxnm0000

Bascom, Rebecca

a. Center for Indoor Air Research P.I. David Swift "Human Inhalability of Ultralarge Particles"
b. P.I.:; 20% effort
c. 01/01/93 - 12/30/95; $233,311
d. 01/01/93 - 12/30/93; $ 73,782
e. Determine the inhalability of particles of sizes from 50-300 um in the human respiratory tract in breathing manikins and human subjects.
f. None.
g. None.

a. U.S. Department of Energy. P.I.- David L. Swift "Regional Aerosol Deposition in Human Upper Airways."
b. P.I.; 40% effort
c. 03/01/94 - 02/28/97; $358,440
d. 03/01/94 - 02/28/95; 122,910
e. Same as current project of same title; this is a continuation of research for a further three years.
f. None; support in this grant will replace support in current grant from U.S.D.O.E.
g. None.

PENDING SUPPORT - David L. Swift, Ph.D.
None.

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Source: https://www.industrydocuments.ucsf.edu/docs/rxnm0000

Thomas Permutt, Ph.D. **OTHER SUPPORT**

Name: Thomas Permutt, Ph.D. Active: ✔ Pending: None:
Source and identifying no.: NIADA, RO1-DA/NS06625-01A1 P.I.: M. Sloan, M.D.
Title: Case-Control Study of Drug Abuse in Stroke
b. Your role on project: Statistician % Effort: 10%
c. Dates and costs of entire project: 10/01/91-09/30/96, $1,281,373
d. Dates and costs of current year: 10/01/91-09/30/92
e. Specific aims of project: To determine if stroke is associated with drug use.
f. Describe scientific and budgetary overlap: None
g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.): None

Name: Thomas Permutt, Ph.D. Active: ✔ Pending: None:
Source and identifying no.: Tag/Teva Pharmaceuticals P.I.: K.P. Johnson
Title: Double-blind Placebo-controlled Phase III Study to Evaluate the Safety and Efficacy of Copolymer I Given Subcutaneously in Patients with Relapsing-remitting Multiple Sclerosis
b. Your role on project: Statistician % Effort: 10%
c. Dates and costs of entire project: 01/01/92-09/30/93
d. Dates and costs of current year: 01/01/92-12/31/92
e. Specific aims of project: To evaluate COP1 in relapsing-remitting multiple sclerosis.
f. Describe scientific and budgetary overlap: None
g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.): None

Name: Thomas Permutt, Ph.D. Active: ✔ Pending: None:
Source and identifying no.: Center for Indoor Air Research, #90-30 P.I.: R. Bascom, M.D.
Title: Environmental Tobacco Smoke: Nasal Response and Aerosol Deposition Effect
b. Your role on project: Statistician % Effort: 5%
c. Dates and costs of entire project: 10/01/90-09/30/93
d. Dates and costs of current year: 10/01/91-09/30/92
e. Specific aims of project: Measure airway response to smoke.
f. Describe scientific and budgetary overlap: None
g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.): None

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Source: https://www.industrydocuments.ucsf.edu/docs/rxnm0000

BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME	POSITION TITLE
REBECCA BASCOM, M.D., M.P.H.	Associate Professor

EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Radcliffe College, Harvard University Cambridge, Mass.	B.A	1975	French Studies
The University of Oregon Health Sciences Portland, Oregon	M.D.	1979	Medicine
Johns Hopkins Sch. Hygiene & Pub.Health	M.P.H.	1985	Env. & Occup. Med.

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

1991-present Associate Professor of Medicine and Director, Environmental Research Facility, The University of Maryland School of Medicine, Baltimore, MD.

1986-1991 Assistant Professor of Pulmonary Medicine and Director, Environmental Research Facility, The University of Maryland School of Medicine, Baltimore, Maryland

1986-present Assistant Professor, The Johns Hopkins School of Medicine

1985-1986 Instructor in Medicine, The Johns Hopkins School of Medicine, Baltimore

1984-1986 Research Fellowship, The Johns Hopkins School of Medicine, Department of Medicine, Division of Clinical Immunology

1982-1985 Joint Fellowship in Pulmonary and Residency in Occupational Medicine, The Johns Hopkins University Department of Medicine and The Johns Hopkins School of Hygiene and Public Health Department of Environmental Health Sciences

1979-1982 Internship & Residency, The Johns Hopkins Hospital, Baltimore, Maryland

HONORS:

1992 State of Maryland Department of the Environment, Environmental Excellence Award

1990 American Lung Association of Maryland, Distinguished Service Award in Environmental and Occupational Health.

EDITORIAL TASKS

1985 - Guest Editor, American Review of Respiratory Diseases, Journal of Allergy and Clinical Immunology, Chest, Journal of the American Medical Association

CONSULTANT AND COMMITTEE ACTIVITIES

1985 American Lung Association of Maryland: Board of Directors (1991 -), Environmental and Occupational Health Committee (Chairman 1989 - present)

1986 American Thoracic Society, (Environmental and Occupational Health Assembly, Long Range Planning Committee, 1990 -)

1986 Maryland State Department of Education, Task Force on Indoor Air Quality

1987 State of Maryland Department of the Environment: Chemical Hypersensitivity Syndrome Study

1988 State of Maryland Governor's Radon Task Force

1990 United States Environmental Protection Agency Data Analysis Team: Indoor Air Quality and Work Environment Study: EPA Headquarters Buildings

1991 American Academy of Allergy and Immunology, Environmental Control and Air Pollution Committee (Chairman)

1991 Institute of Medicine, Committee on the Health Effects of Indoor Allergens

1992 Health Effects of Outdoor Air Pollution. A writing committee of the American Thoracic Society Environmental and Occupational Health Committee (Chairman).

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Biographical Sketch, 2nd page

PUBLICATIONS (selected)

1. Green DJ, Sauder LR, Kulle TJ, Bascom R. Acute pulmonary effects of 3.0 ppm formaldehyde in exercising healthy nonsmokers and asthmatics. Am Rev Respir Dis 1987; 135:1261-6.
2. Bascom R, Pipkorn U, Lichtenstein LM, Naclerio RM. The influx of inflammatory cells into nasal washings during the late response to antigen challenge: Effect of systemic steroid pretreatment. Am Rev Respir Dis 1988; 138:406-412.
3. Freeland HS, Pipkorn U, Schleimer RP, Bascom R, Lichtenstein LM, Naclerio RM, Peters SP. Leukotriene B_4 as a mediator of early and late reactions to antigen in humans: The effect of systemic glucocorticoid treatment in vivo. J Allergy Clin Immunol 1989; 83:634-642.
4. Goings S, Kulle T, Bascom R, Sauder L, Green D, Hebel R, Clements ML. Effect of NO_2 exposure on susceptibility to influenza A virus in healthy adults. Am Rev Respir Dis 1989; 139:1075-1081.
5. Bascom R, Pipkorn U, Proud D, Dunnette S, Gleich GJ, Lichtenstein LM, Naclerio RM. Major basic protein and eosinophil-derived neurotoxin concentrations in nasal lavage fluid after antigen challenge: effect of systemic corticosteroids and relationship to eosinophil influx. J Allergy Clin Immunol 1989; 84:338-346.
6. Churchill L, Chilton FH, Resau JH, Bascom R, Hubbard WC, Proud D. Cyclooxygenase metabolism of endogenous arachidonic acid by cultured human tracheal epithelial cells. Am Rev Respir Dis 1989; 140:449-459.
7. Green D, Bascom R, Healey E, Hebel JR, Sauder L, Kulle T. Acute pulmonary response in healthy, nonsmoking adults to inhalation of formaldehyde and carbon. J Toxicol Environ Health 1989; 28:261-275.
8. Bascom R, Naclerio RM, Fitzgerald TK, Kagey-Sobotka A, Proud, D. Effect of ozone inhalation on the response to nasal challenge with antigen of allergic subjects. Am Rev Respir Dis 1990; 142:594-601.
9. Bascom R, Kulle T, Kagey-Sobotka A, Proud D. Upper respiratory tract environmental tobacco smoke sensitivity. Am Rev Respir Dis 1991; 143:1304-1311.
10. Bascom R, Kagey-Sobotka A, Proud D. Effect of intranasal capsaicin on symptoms and mediator release. J Pharmacol Exp Ther 1991; 259:1323-1327.
11. Bascom R. The upper respiratory tract: mucous membrane irritation. Env Health Perspect 1991; 95:39-41.
12. Willes S, Raford P, Baroody F, Fitzgerald TK, Bascom R. Differential responses to ozone in allergic and non-allergic subjects. Am Rev Respir Dis 1991; 143:A91.
13. Baroody F, Raford P, Willes S, Fitzgerald TK, Naclerio RM, Bascom R. The effect of ozone on the nasal response to methacholine (mc) in allergic and nonallergic subjects. Am Rev Respir Dis 1991, 143:A93.
14. Bascom R. Differential responsiveness to tobacco smoke: possible mechanisms. Pharmocogenetics 1991; 1:102-106.
15. Bascom R. Differential responsiveness to irritant mixtures: possible mechanisms. Annal NY Acad Sci 1992; 641:225-247.
16. Raford P, Bascom R. Disorders of the Upper Airway. Textbook of Clinical and Occupational Medicine, Cullen MR, Rosenstock L eds. W.B. Saunders, 1992. In press.
17. Bascom R. Air Pollution and the Nose. Allergic and Non-Allergic Rhinitis: Clinical Aspects. Naclerio RM, Mygind N eds. 1992. In Press.
18. Indoor Allergens: Assessing and Controlling Adverse Health Effects. A report of the Committee on the Health Effects of Indoor Allergens. A committee of the Institute of Medicine. Bascom R, committee member. In preparation.
19. Bascom R, Ford E. Don't just "do spirometry" -- Closing the loop in workplace spirometry programs. In: Beckett WS, Bascom R, eds. Occupational Medicine: State of the Art Reviews. Philadelphia: Hanley & Belfus, Inc. 1992: 7:331-345.
20. Willes S, Fitzgerald T, Bascom R. Nasal inhalation challenge studies with sidestream tobacco smoke. Arch Environ Health 1992; 47:223-230.
21. Nadarajah J, Bascom R, Fitzgerald TK, Bickert M, Cheng K, Permutt T, Swift D. Sidestream tobacco smoke (SS) alters regional nasal mucociliary clearance: comparison of sensitive and nonsensitive subjects. Submitted 1992. Am Rev Respir Dis.

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

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R: REDACTED MATERIAL

Principal Investigator/Program Director: Bascom, Rebecca

BIOGRAPHICAL SKETCH

NAME	TITLE	BIRTHDATE
David L. Swift	Professor	REDACTED

INSTITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
Purdue University, Lafayette, IN	B.S.	1957	Chemical Eng.
Mass. Inst. of Tech., Cambridge, MA	S.M.	1959	Chemical Eng.
Johns Hopkins University, Balto, MD	Ph.D.	1963	Chemical Eng.
London School of Hygiene, England	Post-Doc.	1966	Aerosol Physics

PROFESSIONAL EXPERIENCE:

1978-Present	Professor, Department of Environmental Health Sciences, Division of Environmental Health Engineering, The Johns Hopkins University School of Hygiene And Public Health, Baltimore, Maryland.
1986-Present	Director, Industrial Hygiene and Safety Program, NIOSH Educational Resource Center. The Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland.
1986-87	Visiting Professor, Danish National Institute of Occupational Health, Copenhagen, Denmark.
1970-78	Associate Professor, Department of Environmental Medicine and Department of Environmental Health, Johns Hopkins University School of Hygiene and Public Health.
1966-70	Assistant Professor, Department of Environmental Medicine, The Johns Hopkins University School of Hygiene and Public Health.
1963-65	Assistant Chemical Engineer, Division of Chemical Engineering, Argonne National Laboratory, Argonne, Illinois.

HONORS AND AWARDS:

Tau Beta Pi, Engineering Honor Society
Delta Omega, Public Health Honor Society
Thompson Visiting Lecturer, London School of Hygiene and Tropical Medicine

PROFESSIONAL SOCIETIES:

American Industrial Hygiene Association
British Occupational Hygiene Society
American Conference of Governmental Industrial Hygienists
American Scientific Affiliation
Gesellschaft fur Aerosolforschung - International Society for Aerosol Research
Sigma Xi - Research Society of America
American Association for Aerosol Research

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PROFESSIONAL SOCIETIES (cont'd)

British Aerosol Society
American Conference of Governmental Industrial Hygienists -
Committee on Air Sampling Instruments

PUBLICATIONS:

Rasmussen, T.R., Swift, D.L., Hilberg, O., and Pedersen, O.F., "Influence of Nasal Passage Geometry on Aerosol Particle Deposition in the Nose". J. Aerosol Medicine, 3, 15-25, (1990).

Breysse, P.N.. and Swift, D.L., "Inhalability of Large Particles into the Human Nasal Passage; In Vivo Studies in Still Air". Aerosol Sci. and Tech., 13, 459-464, (1990).

Cheng, Y-S, Yamada, Y, Yeh, H-C, and Swift, D.L., "Deposition of Ultrafine Aerosols in a Human Oral Cast". Aerosol Sci. and Tech. 12, 1075-1081, (1990).

Swift, D.L., "Experimental Studies of Inertial Aerosol Deposition in Human Upper Airway Casts: Implications for the Proposed NCRP Lung Model". Rad. Prot. Dos., 38, 29-34, (1991).

Cheng, Y-S, Yeh, H-C, and Swift, D.L., "Aerosol Deposition in Human Head Airways for Particles 1 nm to 20 um". Rad. Prot. Dos., 38, 41-47 (1991).

Phelan, R.F., Cuddihy, R.G., Fisher, G.L., Moss, O.R., Schlessinger, R.B., Swift, D.L. and Yeh, H-C, "Main Features of the Proposed NCRP Respiratory Tract Model". Rad. Prot. Dos., 38, 179-184, (1991).

Becquemin, M.H., Swift, D.L., Bouchikhi, A., Roy, M. and Teillac, A., "Particle Deposition in the Noses of Adults and Children". Eur. Resp. J., 4, 694-702, (1991).

Gonda, I. and Swift, D.L., "Losses of Gallium in Common Laboratory Ware and Ways to Minimize Them". Eur. J. Nucl. Med., 18, 511-513, (1991).

Swift, D.L., Montassier, N., Hopke, P., Karpen-Hayes, K., Cheng, Y-S, Su, Y-F, Yeh, H-C and Strong, J.C., "Deposition of Ultrafine Particles in Human Nasal Replicate Casts". J. Aerosol Sci., 23, 65-72, (1992).

Swift, D.L., "Apparatus and Method for Measuring Regional Distribution of Therapeutic Aerosols and Comparing Delivery Systems" J. Aerol Sci., 23 Suppl. 1, S495-S498 (1992).

Cheng, Y.S., Su, Y.F., Yeh, H.C. and Swift, D.L., "Deposition of Thoron Progeny in the Human Head Airways". Aerosol Sci. and Tech., In Press, 1992.

Yeh, H.C., Cuddihy, R.G., Fisher, G.L., Moss, O.R., Phelan, R.F., Schlessinger, R.B. and Swift, D.L., "The Proposed NCRP Respiratory Tract Model" in Proceedings of the First Symposium on Pollution and Health Effects", Taipei, Taiwan, Sept. 10-12, 1991, In Press, 1992.

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BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants listed on page 2. Begin with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	POSITION TITLE	BIRTHDATE (Mo., Day, Yr.)
Thomas Permutt, Ph.D.	Assistant Professor	R

EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Cornell University, Ithaca NY	A.B.	1974	Mathematics
University of Cambridge, England	Diploma	1975	Statistics
University of California, Berkeley	M.A.	1978	Economics
University of California, Berkeley	Ph.D.	1984	Statistics

RESEARCH AND PROFESSIONAL EXPERIENCE. Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

RESEARCH AND PROFESSIONAL EXPERIENCE

1974	Statistician: U.S. Bureau of the Census, Washington, D.C.
1978-1982	Acting Instructor in Statistics: University of California, Berkeley
1983-1985	Visiting Assistant Professor of Statistics: University of Iowa, Iowa City
1985-1988	Senior Statistician: Systems Applications, Inc., San Rafael, California
1988-present	Assistant Professor of Epidemiology and Preventive Medicine: School of Medicine, University of Maryland at Baltimore

AFFILIATIONS

Member, American Statistical Association Committee on Energy Statistics (Advisory Committee to Energy Information Administration)

PUBLICATIONS

Permutt T, Hebel JR: Simultaneous-equation estimation in a clinical trial of the effect of smoking on birth weight. *Biometrics* 1989;45:619-622.

Permutt T: Testing for imbalance of covariates in controlled experiments. *Statistics in Medicine* 1990;9:1455-1462.

Permutt T, Edland SD, Moezzi M, Grosser SG: Likelihood techniques for interlaboratory calibration in the National Stream Survey. *Journal of Chemometrics* 1991;5:299-308.

Rosenthal GL, Wilson PD, Permutt T, Boughman J, Ferencz C: Birth Weight and Cardiovascular Malformations: A Population-based Study. *American Journal of Epidemiology* 1991:133:1273-1281.

Burns BJ, Taube JE, Permutt T, Rudin SC, Mulcare ME, Harbin HT and Goldman HH: A fiscan incentive to nursing homes for placing state hospital patients. *Hospital and Community Psychiatry* (to appear).

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Bascom, Rebecca

UIC The University of Illinois at Chicago

College of Medicine
Department of Medicine
Section of Environmental and Occupational Medicine (M/C 788)
220 Goldberg Research Center
1940 West Taylor Street
Chicago, Illinois 60612-7393
(312) 996-3003 Fax: (312) 996-1286

Donovan B. Yeates, PhD
Research Professor, Chief

Stephen M. Hessl, MD, MPH
Associate Professor and Associate Chief
Director, Occupational
Medicine Residency Program
(312) 996-1063

Linda S. Forst, MD, MPH
Director, Environmental
and Occupational Medicine
Clinical Services
(312) 996-1063

Jeffrey E. Coe, MD, PhD
Ronald A. Harrison, MD; PhD
Anthony J. Hickey, PhD
Roy Lacey, DO, MPH
Yannick M. LeGuyader, MD, MPH
Irving F. Miller, PhD
Peter Orris, MD, MPH
Marie-Claude Rigaud, MD MPH
Pamela Strauss, MD, MPH
Lid B Wong, PhD

May 27, 1993

Rebecca Bascom, M.D.
Pulmonary Division
University of Maryland
10 S. Pine Street - Mstf-800
Baltimore, Maryland 21201-1192

Dear Dr. Bascom,

I am delighted to be a consultant on your grant, "Mucociliary Clearance: a Biomarker of Sensitivity to Sidestream Tobacco Smoke?". The mucociliary clearance system has been shown to be a very sensitive indicator of inhaled irritants. Tobacco smoke has a number of mediators and agents that could both activate and inhibit this system in the nasopharynx. I believe that working with you and Dr. David Swift on this could both help interpret the mechanisms, whereby your observed results may be mediated, and help us to determine what further mechanistic studies should be conducted in our animal models. I also believe the involvement of Dr. Wong in this project, will add additional worthwhile expertise, especially in terms of his superior technological expertise, and his insight into the intra- and intercellular mechanisms regulating ciliary beat frequency.

I am looking forward to this exciting and mutually beneficial interaction.

Sincerely,

Donovan B. Yeates

Donovan B. Yeates, Ph.D.

DBY
Encl.

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BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME	POSITION TITLE
Donovan B. Yeates, Ph.D.	Research Professor of Medicine

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Perth Technical College, W. Australia	Assoc. AP	1967	Applied Physics
University of Surrey, England	M.Sc. (D)	1969	Radiation Physics
University of Toronto, Canada	Ph.D.	1975	Medical Biophysics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

1992-present Professor, College of Engineering, Program in Bioengineering, University of Illinois at Chicago
1992-present Associate Research Career Scientist-Research Physiologist, GM-15, VA Medical Center, West Side, Chicago, Illinois
1989-Present Research Professor of Medicine, Department of Medicine, University of Illinois at Chicago.
1989-Present Chief, Section of Environmental and Occupational Medicine, University of Illinois at Chicago.
1988-1990 Director, Occupational Health and Safety Center of the University of Illinois at Chicago (Acting Director: 1987-88).
1987-1989 Associate Chief, Section of Environmental and Occupational Medicine, Department of Medicine, University of Illinois at Chicago.
1982-Present Member of the Graduate College, University of Illinois at Chicago.
1981-Present Research Physiologist, GS-14, VA West Side Medical Center, Chicago.
1978-1989 Research Associate Professor, Department of Medicine, University of Illinois at Chicago.
1978-1987 Associate Director, Section of Environmental Medicine, Department of Medicine, University of Illinois at Chicago.
1978-1981 Research Physiologist, GS-13, VA West Side Medical Center, Chicago
1976-1978 Assistant Professor, Institute of Environmental Medicine, New York, University Medical Center, New York, New York.

HONORS: Master of Science Degree with Distinction, 1969
Rotary Foundation Award for Technical Training, Rotary International: 1969-1970
Fellow of the Canadian Cystic Fibrosis Foundation: 1972-1974
Veteran's Administration, Outstanding Performance: 1983, 1988, 1991
Veteran's Administration, Associate Research Career Scientist: 1987-1992, 1992-1997

SELECTED PUBLICATIONS: Some relevant earlier publications and the past three years

1. Lippmann, M., Yeates, D.B. and Albert, R.E. Deposition, retention, and clearance of inhaled particles. Brit J Indus Hyg, 37:337-362, 1980.
2. Venizelos, P.C. Gerrity, T.R. and Yeates, D.B. Response of human mucociliary clearance to acute alcohol administration. Arch Environ Hlth, 36(4):194-201, 1981.
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22. Pillai, R.S., Chandra, T., Miller, I.F., Lloyd-Still, J. and Yeates, D.B. Work of adhesion of respiratory tract mucus. J Appl Physiol, 72(4):1604-1610, 1992.
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25. Chandra, T., Miller, I.F. and Yeates, D.B. A pore transport model for pulmonary alveolar epithelium. Annals of Biomedical Engineering, 20(4):461-492, 1992.
26. Wong, L.B. and Yeates, D.B. Luminal purinergic regulatory mechanisms of tracheal ciliary beat frequency. Amer J Respir Cell Mol Biol, 7:447-454, 1992.
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Irving F. Miller, PhD
Peter Orris, MD, MPH
Marie-Claude Rigaud, MD, MPH
Pamela Strauss, MD, MPH
Lid B. Wong, PhD

May 27, 1993

Rebecca Bascom, M.D.
Pulmonary Division
University of Maryland
10 S. Pine St - Mstf-800
Baltimore, Maryland 21201-1192

Dear Dr. Bascom:

I am pleased to be a consultant on your grant entitled "Mucociliary Clearance; Biomarker of Sensitivity to Sidestream Tobacco Smoke?". The proposal addresses important questions and offers exciting opportunities for exploring the answer for one of the fundamental defensive mechanisms of upper respiratory tract, the nasal mucociliary clearance system. I am delighted for this collaboration that my ongoing research, using cellular engineering techniques in delineating the inter- and intra-cellular regulation of metachronal wave, and ciliary beat frequency, could provide additional insights and interpretations of your research.

I am looking forward to working with you on this exciting project.

Sincerely,

L. B. Wong

Lid B. Wong, Ph.D.

LBW
Encl.

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FF Principal Investigator/Program Director (Last, first, middle): Bascom, Rebecca

BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME	POSITION TITLE
Lid B. Wong, Ph.D.	Research Assistant Professor

EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Southern Illinois University, Carbondale	B.A.	1978	Physiology
Southern Illinois University, Carbondale	M.S.	1980	Biological Sciences
University of Illinois, Chicago	Ph.D.	1987	Bioengineering

RESEARCH AND PROFESSIONAL EXPERIENCE. Concluding with present position, list, in chronological order, previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

1993-present Associate Professor, Bioengineering, College of Engineering, University of Illinois, Chicago, Illinois
1989-present Research Assistant Professor, Department of Medicine, University of Illinois, Chicago, Illinois
1987-1989 Research Instructor, Department of Medicine, University of Illinois, Chicago, Illinois

PUBLICATIONS:

1. Dreidner, R.D. and Wong, L.B. Measurements of Ciliary Beat Frequency Using High Speed Video Microscopy. Transactions, ISA., 24(1):33-36, 1985.
2. Hennessy, S.J., Wong, L.B., Yeates, D.B. and Miller, I.F. Automated Measurement of Ciliary Beat Frequency. J. Appl. Physiol., 60(6):2109-2113, 1986
3. Wong, L.B., Miller, I.F. and Yeates, D.B. Stimulation of Ciliary Beat Frequency by Autonomic Agonists: In Vivo. J. Appl. Physiol., 65(2):971-981, 1988.
4. Wong, L.B., Miller, I.F. and Yeates, D.B. Regulation of Ciliary Beat Frequency by Autonomic Agonists: In Vitro. J. Appl. Physiol., 65(4):1895-1901, 1988.
5. Wong, L.B. and Yeates, D.B. Stimulation of Tracheal Ciliary Beat Frequency by Localized Tissue Incision. J. Appl. Physiol., 68(1):411-416, 1990.
6. Wong, L.B., Miller, I.F. and Yeates, D.B. Regulatory Pathways for the Stimulation of Canine Tracheal Ciliary Beat Frequency by Bradykinin. J. of Physiol. (London), 422:421-431, 1990.
7. Wong, L.B., Miller, I.F. and Yeates, D.B. Stimulation of Tracheal Ciliary Beat Frequency by Capsaicin. J. Appl. Physiol., 68(6):2574-2580, 1990.
8. Wong, L.B., Miller, I.F. and Yeates, D.B. Pathways of Substance P Stimulation of Canine Tracheal Ciliary Beat Frequency. J. Appl. Physiol., 70(1):267-273, 1991.
9. Harrison, R.A., Wong, L.B. and Yeates, D.B. Short Term Interaction of Airway and Tissue Oxygen Tensions on Ciliary Beat Frequency. Am. Rev. Respir. Dis., 146:141-147, 1992.
10. Hamelster, H.M., Wong, L.B. and Yeates, D.B. Tracheal Ciliary Beat Frequency in Baboons: Effect of Peripheral Histamine and Capsaicin. Agents Actions, 35:200-207, 1992.
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12. Wong, L.B. and Yeates, D.B. Luminal Purinergic Regulatory Mechanisms of Tracheal Ciliary Beat Frequency. Am. J. Respir. Cell. Molecular Biology, 7:447-454, 1992.
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15. Eljamal, M., Wong, L.B. and Yeates, D.B. Capsaicin Activated Bronchial and Alveolar Initiated Pathways Regulating Tracheal Ciliary Frequency. Submitted.
16. Chandra, T., Yeates, D.B., Miller, I.F. and Wong, L.B. Regulation of Magnitude and Periodicity of Canine Tracheal Ciliary Beat Frequency In Vivo: Stationary and Non-stationary Correlation-Frequency Analysis of Heterodyne Laser Light Scattering. In Preparation
17. Chandra, T., Mussatto, D.J., Yeates, D.B. and Wong, L.B. Histamine Challenge Induces Low Order Chaotic Respiratory Rhythm to Change to Periodic Behavior Through the Intermittence Route. In Preparation.
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19. Chandra, T., Yeates, D.B. and Wong, L.B. Millisecond Time Scale Measurement of Tracheal Ciliary Beat Frequency on TMS320C30 Digital Signal Processor. In Preparation.

ABSTRACTS:

1. Chandra, T., Wong, L.B., Miller, I.F. and Yeates, D.B. Periodicity of Tracheal Ciliary Beat Frequency In Vivo. The Physiologists, 34(4):236, 1991.
2. Wong, L.B. and Yeates, D.B. Intracellular IP_3 Activated Calcium-Calmodulin Oscillator Regulates An Alpha 1 Adrenergic Induced Periodic Behavior of Ciliary Beat Frequency *In Vivo*. Clin. Res., 1991.
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4. Chandra, T., Wong, L.B., Mussatto, D.J. and Yeates, D.B. Histamine Challenge Induces Low Order Chaotic Respiratory Rhythm to Change to Periodic Behavior Through the Intermittence Route. The FASEB J., 1992.
5. Hameister, W.M., Chandra, T., Wong, L.B. and Yeates, D.B. Reflex Inhibition of Tracheal Ciliary Beat Frequency Following Nicotine Inhalation in Baboons and Dogs. The FASEB J., 1992.
6. Mussatto, D.J., Daza, A.V., Hameister, W.M., Chandra, T., Wong, L.B and Yeates, D.B. Does Histamine Induce Bronchoconstriction Independently Through Alveolar and Bronchial Initiated Mechanisms and Are There Concomitant Changes in Tracheal Ciliary Beat Frequency? Am. Rev. Respir. Dis., 145(4) (part 2 of 2 parts):A380, 1992.
8. Wong, L.B. and Yeates, D.B. Alpha 1 Receptor Regulates the Periodicity of Tracheal Ciliary Beat Frequency (CBF) *in vivo* Through Calmodulin. Am. Rev. Respir. Dis., 145(4) (part 2 of 2 parts):A355, 1992.
9. Yeates, D.B., Wong, L.B. and Miller, I.F. Mechanisms of Tracheobronchial Mucociliary Transport. AIChE, 396:167A, 1992.
10. Mussatto, D.J., Daza, A.V., Hameister, W.M., Chandra, T., Wong, L.B. and Yeates, D.B. Moderate Bronchoconstrictive Response in Dogs to Histamine Induced Through Vagal and Direct Pathways. Clin. Research, 40(3):697A, 1992.
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13. Wong, L.B. and Yeates, D.B. Adenylate Cyclase-cAMP Dependent Organization of Ciliary Beat Frequency (CBF). The FASEB J., 7(3) (part 1):A357, 1993.
14. Yeates, D.B. and Wong, L.B. Regulation of Magnitude and Periodicity of Ciliary Beat Frequency and Metachronal Wave Period. XXXII Int. Congress of Physiol. Sciences, 1993. Submitted.

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University of Maryland Medical Center

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OFFICE OF THE DEAN
Institutional Review Board
Institutional Animal Care and Use Committee

MEMORANDUM

TO: *Rebecca Bascom, Principal Investigator*

FROM: *Institutional Review Board*
Assurance Number M1174-01NR

DATE: *May 27, 1993*

RE: *"Sidestream Tobacco Smoke and Mucociliary Clearance"*
(Center for Indoor Air Research)

The above-referenced project is incorporated into a protocol on file with this Committee entitled, "Respiratory Sensitivity to Environmental Tobacco Smoke", under your direction (684886-099201). This protocol was given approval September 4, 1992 and last amended April 1, 1993. An amendment is pending review for the July meeting of the IRB. You will be advised of the Board's decision.

If the above project is altered in any way, please notify the IRB office. Please retain a copy of this letter for your records. If you have any questions, please do not hesitate to contact Joe Giffels, IRB Coordinator, at 706-5037.

David A. Van Echo

David Van Echo, Chairman
Institutional Review Board

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SCHEMATIC DESCRIPTION OF AIMS FOR CIAR PROPOSAL
R. Bascom and D. Swift June 1, 1993

AIM 1: To characterize the effect of SS exposure on mucociliary clearance with respect to its spatial distribution and intrasubject reproducibility.

TASK #1-A: Redesign the scintillation detector for simultaneous face and anterior-posterior collimated measurements

Timeline: 4 months

TASK #1-B: Profile tantalum clearance in the anterior nose following clean air and SS exposure, correlating with contralateral measurements using the scintillation method.

N= 16 (8 ETS-sensitive 8 ETS-nonsensitive)

Exposure: two exposures, at least two weeks apart: clean air or SS (15 ppm CO) for one hour at rest

Protocol:

Time(minutes):	0	30	60	90	120	180	240
SYMPTOMS	X X	X X X	X	X			
EQUILIBRATION		———					
EXPOSURE			———				
99mTC-SULFUR COLLOID AEROSOL ADMINISTRATION						X	
CLEARANCE MEASUREMENTS						//////////	
TANTALUM ADMINISTRATION						X	
NASAL VINYL POLYSILOXANE IMPRESSION							X

TASK 1-C: Determine the reproducibility of the effect of SS on mucociliary clearance

N=16, (8 ETS-sensitive, 8 ETS-nonsensitive [Note: the same subjects will be used as in TASK #1-B])

Exposure: one day, at least two weeks after Protcol#1-B; SS (15 ppm CO) for one hour at rest with comparison to the results from Protocol #1-B

Protocol:

Time(minutes):	0	30	60	90	120	180	240
SYMPTOMS	X X	X X X	X	X			
EQUILIBRATION		———					
EXPOSURE			———				
99mTC-SULFUR COLLOID AEROSOL ADMINISTRATION						X	
CLEARANCE MEASUREMENTS						//////////	

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AIM 2: To determine the exposure-response characteristics of altered mucociliary clearance in the upper respiratory tract following sidestream tobacco smoke exposure in ETS-sensitive and ETS-nonsensitive subjects.

N= 16 8 ETS-sensitive, SS previously shown to inhibit mucociliary clearance
8 ETS-nonsensitive, SS previously shown to accelerate mucociliary clearance

Exposure: four separate days, each separated by two weeks
clean air, SS (1,5,15 ppm CO) for one hour at rest

Protocol:

Time(minutes):	0	30	60	90	120	180	240
SYMPTOMS	X	X	X	X	X	X	X
EQUILIBRATION	———						
EXPOSURE			———				
AEROSOL ADMINISTRATION					X		
CLEARANCE MEASUREMENTS					////	////	

AIM 3: To determine the time-response characteristics of altered mucociliary clearance in the upper respiratory tract following sidestream tobacco smoke exposure in ETS-sensitive and ETS-nonsensitive subjects.

SUBJECTS: N= 16
8 ETS-sensitive, SS previously shown to inhibit mucociliary clearance
8 ETS-nonsensitive, SS previously shown to accelerate mucociliary clearance

Time(minutes):	0	30	60	90	120	180	240
SYMPTOMS	x	x	x	x	x	x	
EQUILIBRATION	———						
EXPOSURE				———	———		
AEROSOL ADMINISTRATION			X				
CLEARANCE MEASUREMENTS	////	////	////	////	////	////	////

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AIM 4: To develop a simple, convenient and objective method, suitable for field studies, to assess mucociliary clearance in the upper respiratory tract.

TASK 4-A:

To select a fluorescent probe for use as a nasal aerosol according to the follwoing criteria:

1. Prior safe use in humans (e.g. sodium fluorescein)
2. Fluorescent profile that provides an acceptable signal above the bakcground of nasal secretions.
3. Clearance profile that resembles that of the 99m Tc-sulfur colloid i.e. it remains on the airway surface, and is cleared rather than absorbed
4. Stable for transport of sample back from the field without refrigeration.

TASK #4-B:

1. To aerosolize the probe into the nose using the Devillbus 40 nebulizer
2. To determine the optimal time and method of nasal lavage for the recovery of the tracer.
3. To goal will be to complete the assay on subjects within 30-45 minutes (consistent with the duration required to perform tests such as skin prick tests and measurements of bronchial hyperreactivity).

TASK #4-C

1. To characterize the fluorescent mucociliary clearance assay with respect to the coefficient of variation for repeated measures, and its consistency over time in a group of ETS-sensitive and ETS-nonsensitive subjects, and to compare results with those obtained with the 99mTc-sulfur colloid assay.

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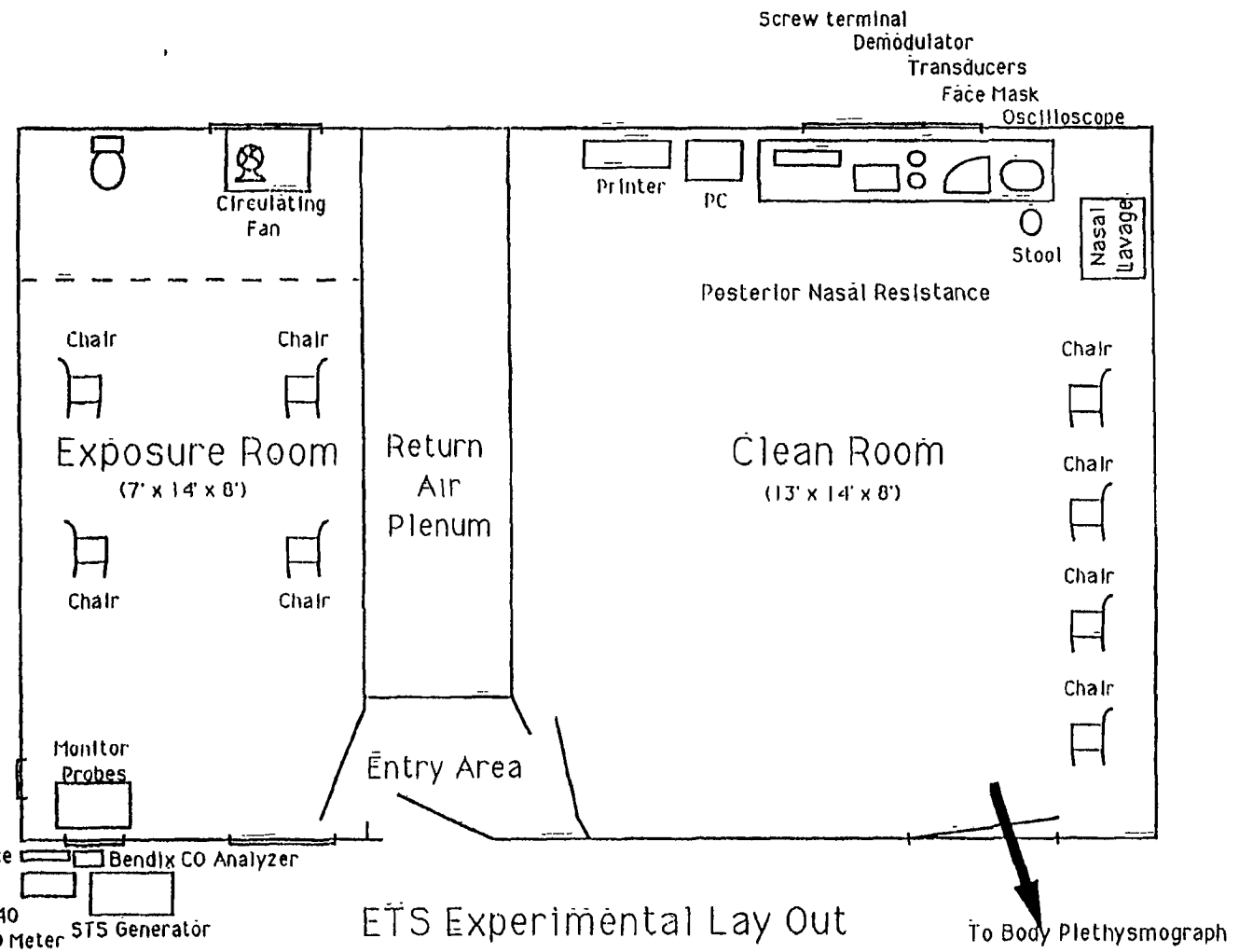

ETS Experimental Lay Out

UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
ENVIRONMENTAL RESEARCH FACILITY

Scale. 1" = 2'

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55

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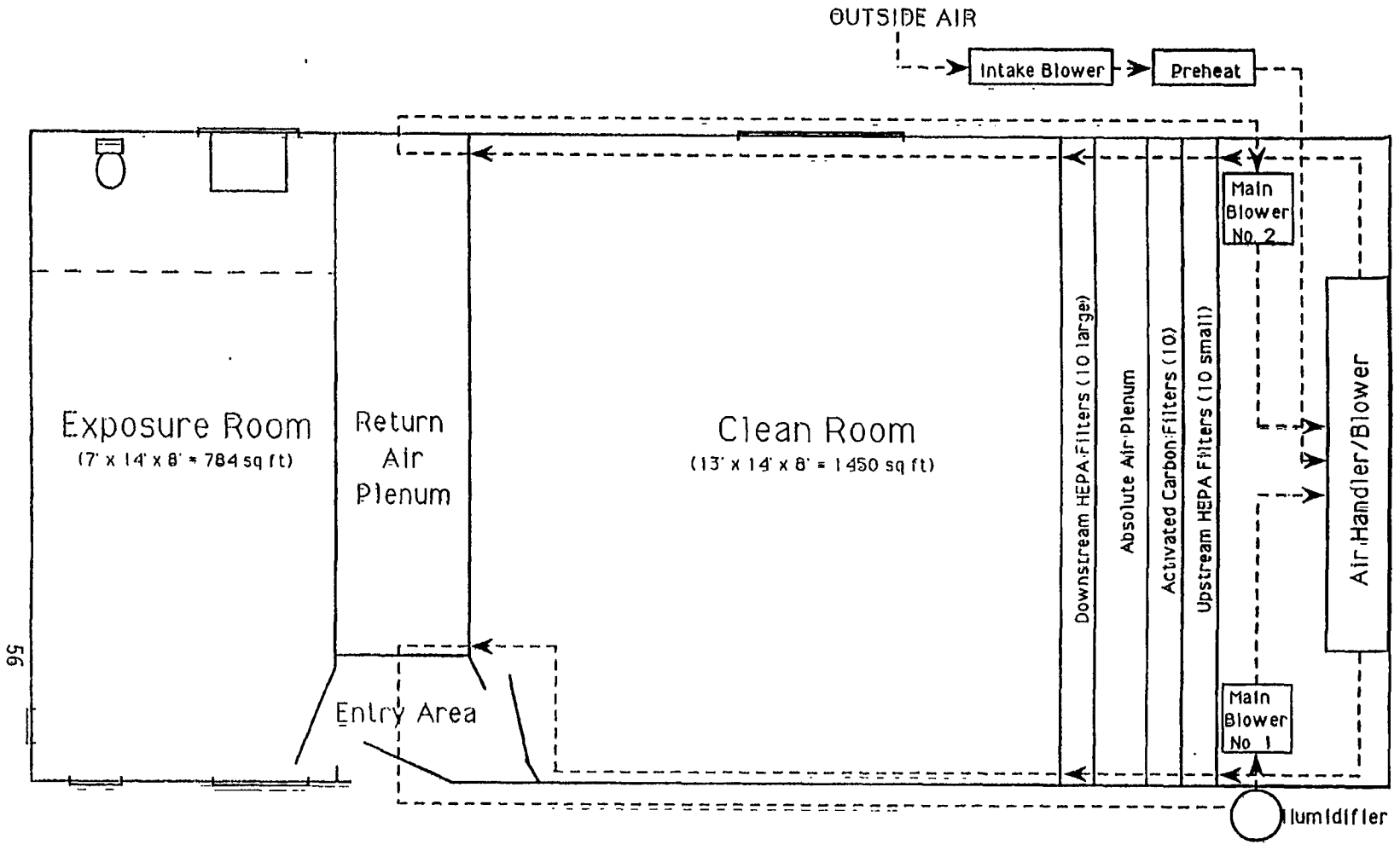

Clean Room Ventilation Scheme (constant airflow)

UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
ENVIRONMENTAL RESEARCH FACILITY

Scale: 1" = 2'

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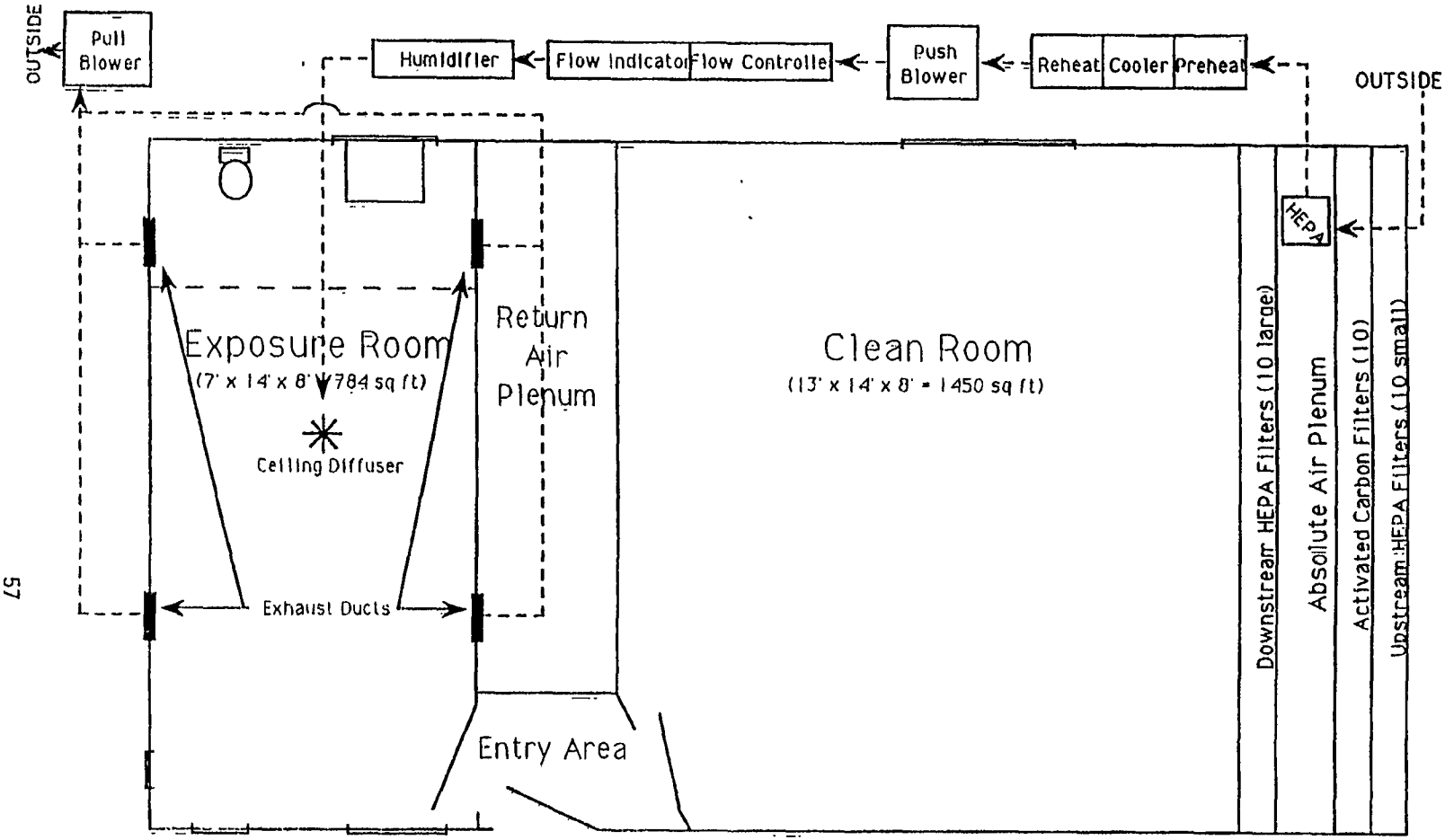

Exposure Room Ventilation Scheme (controlled airflow)

UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
ENVIRONMENTAL RESEARCH FACILITY

Scale: 1" = 2'

57

Bascom, Rebecca

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